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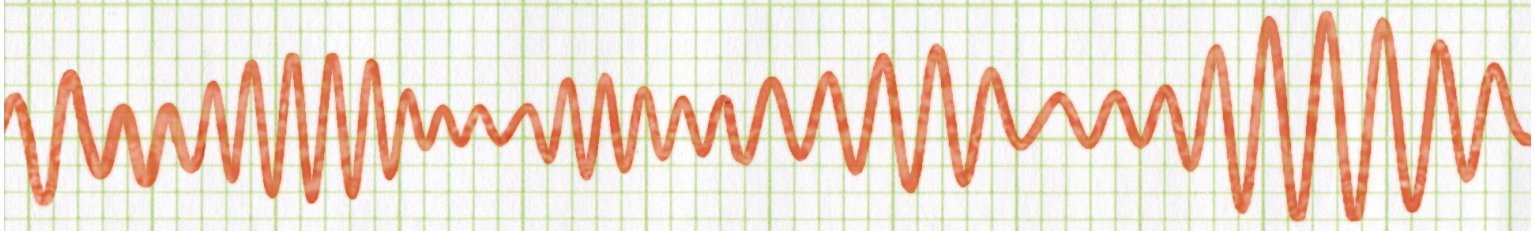
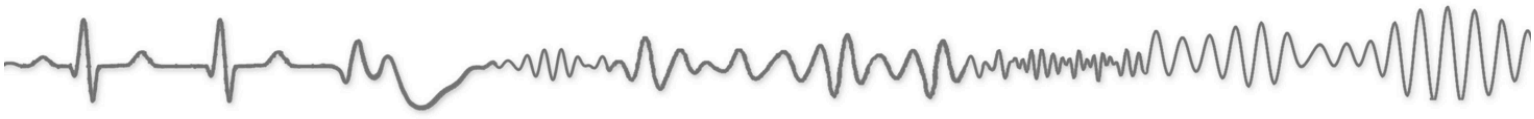


Marleen Bink

SHIFTING ATTENTION TO NEUROFEEDBACK: PSYCHOPHYSIOLOGY IN ADOLESCENTS WITH ADHD AND AUTISM SPECTRUM DISORDERS

M. Bink



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Shifting Attention to Neurofeedback: Psychophysiology in Adolescents with ADHD and Autism Spectrum Disorders

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CHAPTER 1

Introduction

"The morbid alterations to which attention is subject, may all be reduced under the three following heads:
1st. The incapacity of attending with a necessary degree of constancy to any one object.
2dly. A total suspension of its effects on the brain."

"The incapacity with a necessary degree of constancy to any one object, almost always arises from an unnatural or morbid sensibility of the nerves, by which means this faculty is incessantly withdrawn from one impression to another." (....)"When born within a person it becomes evident at a very early period of life, and has a very bad effect, inasmuch as it renders him incapable of attending with constancy to any one object of education"
Crichton (1798), p. 270-271

GENERAL INTRODUCTION

Attention problems are a core feature in adolescents with Attention Deficit /Hyperactivity Disorder (ADHD) as well as in adolescents with comorbid autism spectrum disorders (ASD) and ADHD (ASD+ADHD). To what extent psychophysiological constructs related to attention problems overlap or differ between ADHD and combined ASD+ADHD is yet unknown. Accordingly, it remains unclear whether current treatment strategies, that are effective in reducing ADHD-symptomatology in ADHD, might have a different effect on psychophysiological parameters in combined ASD+ADHD and as a consequence might be less effective.

Neurofeedback is proposed as an intervention that is potentially effective in reducing ADHD- symptomatology. Neurofeedback aims to alter brain activity by operant conditioning and simultaneously reduce ADHD symptoms, mainly to improve attention. However, results to date have been inconsistent and large scale randomized clinical trials are scarce, and the additional effects of neurofeedback in adolescents with ADHD and comorbid disorders have not been investigated. Therefore, this thesis consists of two parts. The first part focuses on psychophysiological overlap and differences between adolescents with ADHD and combined ASD+ADHD. The focus of the second part is on whether it is possible to improve behavioral and neurocognitive functioning in these adolescents with neurofeedback.

ADHD and Autism Spectrum Disorders

In the 18th century, Sir Alexander Crichton was the first to describe a disorder similar to Attention Deficit/Hyperactivity Disorder (ADHD) (Lange, Reichl, Lange, Tucha, & Tucha, 2010). Nowadays, ADHD is defined as patterns of frequent inattention and/or hyperactivity-impulsivity symptoms that interfere with developmentally appropriate social, academic, or occupational functioning (American Psychiatric Association, 2013). ADHD is the most common neurodevelopmental disorder with a worldwide prevalence of around 5% (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007; Willcutt, 2012). Comorbid neurodevelopmental conditions such as learning disabilities, conduct disorder, depression and anxiety are seen more often in youngsters with ADHD than in youngsters without ADHD (Larson, Russ, Kahn, & Halfon, 2011). Additionally, in ASD, which are characterized by persistent problems with social interaction, communication and/or display stereotyped behavior, interests and activities (American Psychiatric Association, 2013), estimations of ADHD comorbidity range between 30% and 78% (Gjevik, Eldevik, Fjaeran-Granum, & Sponheim, 2011; Lee & Ousley, 2006; Simonoff et al., 2008). Notwithstanding the high rates of ADHD comorbidity in ASD, in the Diagnostic and Statistical Manual of Mental Disorders, the DSM-IV (American Psychiatric Association, 2000), ADHD could not be classified as a comorbid disorder of ASD, but ADHD symptoms were considered part of ASD. In order to prevent children with ASD and ADHD symptoms being excluded from potentially beneficial treatment for ADHD (American Psychiatric Association, 2012), the DSM-V

now states that when criteria of ASD and ADHD are met, both diagnoses should be assigned (American Psychiatric Association, 2013).

Currently, best practices for treatment of ADHD symptoms consist of stimulant-medication, and/or behavioral therapy. Evidence of effectiveness of non-pharmacological interventions as behavioral therapies is limited (Sonuga-Barke et al., 2013). Behavioral therapies seem effective for reducing ADHD problems when evaluated by parents or others aware of the received treatment (Sonuga-Barke et al., 2013). However, with blinded assessments these effects disappear (Sonuga-Barke et al., 2013). Stimulant-medication is effective in reducing ADHD symptoms in youngsters with ADHD (Faraone & Buitelaar, 2010; Greenhill et al., 2001). It is effective treatment for ADHD in youngsters with combined ADHD and ASD, although possible to a lesser extent (Cortese, Castelnau, Morcillo, Roux, & Bonnet-Brilhault, 2012; Research Units on Pediatric Psychopharmacology (RUPP) Autism Network, 2005). Moreover, previous studies are inconclusive on whether psychophysiological correlates are different for ASD+ADHD compared to ADHD. Consequently, it is not known whether stimulant medication that seems effective for ADHD treatment (Faraone & Buitelaar, 2010; Greenhill et al., 2001) results in comparable psychophysiological effects in combined ASD+ADHD. Differences in psychophysiology indicate that stimulant-medication might exert its effect differently in combined ASD+ADHD and could possibly help to explain why stimulant-medication seems to be less effective in ASD+ADHD than in ADHD.

Even though stimulant medication seems effective in reducing ADHD symptoms for a large number of youngsters with ADHD (Cortese et al., 2012; Faraone & Buitelaar, 2010; Greenhill et al., 2001; RUPP, 2005), dose-dependent mild adverse effects of stimulant-medication, such as decreased appetite, difficulty falling asleep and headaches, are reported relatively often (Cortese et al., 2012; Graham & Coghill, 2008; RUPP, 2005). Moreover, eventually, the majority of adolescents above the age of 15 discontinue stimulant-medication use, despite the persistent course of the disorder (Zetterqvist, Asherson, Halldner, Langstrom, & Larsson, 2012). Therefore, additional interventions to the current treatment as usual (TAU) to further reduce ADHD symptoms enduringly are warranted. In this respect, neurofeedback has been suggested as a potential effective intervention in reducing ADHD symptoms by modifying brain activity in ADHD (Lofthouse, Arnold, Hersch, Hurt, & DeBeus, 2012; Moriyama et al., 2012) and ASD (Holtmann et al., 2011). Since working mechanisms of interventions, such as stimulant medication and neurofeedback, are (hypothesized to be) based on adapting deviant physiological patterns, it is of importance to understand how physiology is related to ADHD symptoms.

Psychophysiology and ADHD symptomatology

Physiological measures have previously been related to ADHD symptomatology. For example, cardiac reactivity has been related to different psychological processes such as attention, behavioral inhibition and social engagement (Porges, 2007) and consequently to key symptoms of ADHD. Specifically, indications for increased parasympathetic activation with lower heart rate (Negrao, Bipath, van der Westhuizen, & Viljoen, 2011) and increased heart rate variability (Borger & van der Meere, 2000; Borger et al., 1999; Negrao et al., 2011) were found in youngsters with ADHD. In addition, electro-encephalogram (EEG) power spectra in ADHD revealed increased theta power (Cortese, 2012; Loo & Makeig, 2012; Snyder & Hall, 2006), and to a lesser extent, decreased beta activity (Cortese, 2012; Snyder & Hall, 2006). At the behavioral level, theta (4-7 Hz) has been negatively related to vigilance and beta (13-30Hz) positively related to attention (Banaschewski & Brandeis, 2007). Accordingly, theta and beta measures lend support for cortical underarousal in ADHD. Similarly, deviant patterns of event-related potential (ERP) activity are seen in youngsters with ADHD (Du et al., 2006; Groom et al., 2010; Hermens et al., 2005; Johnstone, Barry, & Clarke, 2013; Pliszka et al., 2007). Compared to typically developing youngsters, ERP components related to attention processing are diminished in amplitude in youngsters with ADHD (Barry, Johnstone, & Clarke, 2003; Johnstone et al., 2013), including the N2, which is associated with stimulus orienting and discrimination (Näätänen, Simpson, & Loveless, 1982), and the P3, which is associated with selective attention and (working) memory capacity (Polich & Herbst, 2000) Collectively, diminished cortical activation levels seem apparent in ADHD across different physiological measures.

Stimulant medication that is effective in reducing ADHD symptoms in youngsters with ADHD (Faraone & Buitelaar, 2010; Greenhill et al., 2001) also seems to partly normalize the aforementioned deviant physiological measures in ADHD. Heart rate increases due to stimulant medication (Hammerness, Perrin, Shelley-Abrahamson, & Wilens, 2011) and becomes more similar in stimulant-medicated youngsters with ADHD and typically developing youngsters (Negrao et al., 2011). Stimulant medication decreases the elevated theta activity as seen in ADHD, while simultaneously increasing beta activity (Clarke, Barry, Bond, McCarthy, & Selikowitz, 2002; Clarke et al., 2003; Hermens et al., 2005; Loo & Barkley, 2005). Similarly, stimulant medication appears to regulate ERP activity, with increased N2 (Pliszka et al., 2007) and P3 (Groom et al., 2010; Hermens et al., 2005) amplitudes after stimulant medication use in adolescents with ADHD. Overall, it seems that stimulant medication use by youngsters with ADHD leads to physiological measures that appear to resemble more those of typically developing youngsters, but do not reach identical activity levels.

It is not clear whether physiological patterns in youngsters with combined ASD and ADHD overlap with physiological patterns seen in ADHD. If physiological measures overlap, this could indicate that treatments that reduce ADHD-symptomatology might work similarly in

youngsters with combined ASD+ADHD. However, in the case that physiological measures related to ADHD-symptomatology differ for youngsters with combined ASD+ADHD, this could indicate that ADHD treatments might work differently or be less effective in youngsters with combined ASD+ADHD.

Neurofeedback: an overview

Neurofeedback is an intervention that intends to alter brain activity by giving feedback of electroencephalogram (EEG) activity to patients. Neurofeedback as an intervention for ADHD was originally derived from animal research with cats. In the sixties, Sterman and Wyrwicka (1967) trained hungry cats to inhibit behavior in order to obtain food. During the period behavior was inhibited, EEG recordings showed increased 12 to 20 Hz activity at the sensorimotor cortex. Therefore, this activity was named sensorimotor rhythm (SMR) (Roth, Sterman, & Clemente, 1967; Sterman & Wyrwicka, 1967). Consequently, by training the cats to inhibit behavior they indirectly increased SMR activity, mainly between 12 to 16 Hz (Roth et al., 1967). In a new experiment, the cats were not trained to inhibit behavior, but the hungry cats received food when the recorded EEG showed SMR activity (Sterman, Wyrwicka, & Roth, 1969). In this way, Sterman, Wyrwicka, et al. (1969) intended to train the SMR activity more directly, instead of training behavior and consequently SMR activity. Note that the cats started to show sets of behavior with typical inhibited postures simultaneously with the SMR activity, in order to obtain food. In a subsequent experiment, three cats that were trained to produce SMR activity, together with three cats that did not receive this training, were poisoned with monomethylhydrazine in an experiment for NASA on the toxic effects of rocket fuel (Sterman, LoPresti, & Fairchild, 1969). Compared to the untrained cats, more monomethylhydrazine was needed for the SMR-trained cats to show epileptic activity. Accordingly, it was concluded that SMR training has protective properties. Moreover, it was hypothesized that it may be possible to train brain regulation enduringly by operant conditioning in humans as well.

Considering the possible protective properties, the first studies of SMR training in humans included epileptic subjects (Sterman & Friar, 1972; Sterman, Macdonald, & Stone, 1974). After long-term (more than two to three months) biofeedback training of the SMR activity, the patients showed a decrease in epileptic activity and displayed SMR activity more often than before the training (Sterman et al., 1974). Taken together, the results indicated that SMR activity (12-16Hz) is related to cortical inhibition (Roth et al., 1967; Sterman & Wyrwicka, 1967; Sterman, Wyrwicka, et al., 1969) and could be trained in humans (Sterman & Friar, 1972; Sterman et al., 1974). Correspondingly, it was reasoned by Lubar and Shouse (1976) that training aimed at increasing SMR activity would improve inhibition problems in children with ADHD. In addition, the training aimed to reduce theta activity that is negatively related to vigilance. After positive results in this case

study, other studies followed with more participants. Until now, the effects of neurofeedback have been investigated and applied mostly in youngster with ADHD.

The most frequently applied neurofeedback protocol for reducing ADHD symptoms is the theta/beta training, which aims to decrease theta (4-7Hz) and increase SMR (12-15Hz) or beta (12-20Hz) (Lofthouse et al., 2012; Loo & Makeig, 2012; Moriyama et al., 2012). This training protocol is based on the assumption that children with ADHD show increased theta activity and decreased beta activity compared with typically developing children (Snyder & Hall, 2006). Theta and beta activity are related to vigilance and attention respectively (Banaschewski & Brandeis, 2007). Correspondingly, the rationale is that a decrease in theta activity would result in improved vigilance and an increase in beta would result in improved attention.

In practice, a neurofeedback training session starts with the attachment of electrodes on the scalp, mostly on the vertex (Cz) with references linked mastoid. The signals are amplified and sent to a computer. Software developed for neurofeedback training converts the incoming signal and the converted signal is made visible on the monitor of the neurofeedback trainer. The trainer looks at the raw EEG-signal and the signal separated in frequency bands between 4Hz and 32 Hz. Several frequency bands can be trained simultaneously. Accordingly, for theta/beta training the software is programmed to reinforce the SMR or beta activity and to inhibit theta activity or other frequency bands. Based on the incoming EEG-signal, the limits per frequency band are determined. When the signal is within the set limits of each frequency bands, then the signal is considered appropriate and the patient is rewarded with positive feedback. At the same time, the patient watches a monitor that displays a visual representation of his/her own brain activity. This visual representation can be presented as a movie or a game like situation. In the case of a movie, the quality of the film as well as the sound, rely on the produced brainwaves. In the game like situation, graphics, sound and score depend on the produced brainwaves. In this way the different frequency bands are reinforced or inhibited by means of operant conditioning in 20 to 40 sessions.

A special kind of neurofeedback is the training of slow cortical potentials (SCPs). SCPs are stimuli related very slow potentials (<0.1 Hz). A negative (downwards curving) very slow brainwave is associated with increased cortical activation and related to more efficient behavioral responses. A positive (upwards curving) very slow brain wave is associated with a decrease of cortical activation and less efficient behavioral responses (Birbaumer, Elbert, Canavan, & Rockstroh, 1990). The idea is basically that the patient gets control to increase and decrease the activation level of the brain. However, implementation of SCP-training in practice is limited, partly because SCPs are harder to measure reliably.

Effectiveness of neurofeedback in ADHD treatment

The first non-randomized effectiveness studies in youngsters with ADHD compared care as usual, including stimulant medication, with neurofeedback, sometimes as additional training to care as usual. Overall, these studies showed comparable improvement in attention, as measured by behavioral questionnaires and neuropsychological tests, for youngsters receiving neurofeedback compared to youngsters receiving stimulant medication (Fuchs, Birbaumer, Lutzenberger, Gruzelier, & Kaiser, 2003; Rossiter & La Vaque, 1995). In addition, neurofeedback seemed of additional value to stimulant medication (Monastra, Monastra, & George, 2002). Compared to a combined treatment of stimulant medication with parent- and school-education, youngsters with ADHD who also received neurofeedback displayed increased brain activity, improved attention and less hyperactive/impulsive behavior at home and at school. The study by Monastra et al. (2002) showed that the youngsters who received neurofeedback one-year post neurofeedback training still displayed less ADHD symptomatology compared to the youngster who received standard treatment.

The randomized studies that followed also showed positive effects after neurofeedback training. The largest randomized study with 94 children between the ages of 8 and 12 years old showed that neurofeedback training (n=59) was more effective in reducing ADHD-symptomatology than computerized attention training (n=35) up to a half-year post treatment (Gevensleben et al., 2010; Gevensleben, Holl, Albrecht, Vogel, et al., 2009). Moreover, the study found changes in brain functioning as reflected in a decrease of posterior-midline theta activity. In addition, the decrease in theta activity was related to the decrease in ADHD symptoms as reported by parents (Gevensleben, Holl, Albrecht, Schlamp, et al., 2009). The study of Duric, Assmus, Gundersen, and Elgen (2012) showed similar improvement in attention on behavioral questionnaires over time for children with ADHD who were treated with neurofeedback (n=30), stimulant medication (n=31) or combined neurofeedback and stimulant medication (n=30). Comparably, a smaller study with a RCT design also showed similar improvement in attention for neurofeedback (n=12) and stimulant medication (n=11) (Meisel, Servera, Garcia-Banda, Cardo, & Moreno, 2013). In line with the positive outcomes of the uncontrolled studies, these RCTs showed comparable improvement for neurofeedback compared to stimulant-medication.

In contrast, blinded RCT's, overall, do not show superiority or neurofeedback over sham-neurofeedback in reducing ADHD-symptoms (Arnold et al., 2012; Perreau-Linck, Lessard, Levesque, & Beauregard, 2010; van Dongen-Boomsma, Vollebregt, Slaats-Willemse, & Buitelaar, 2013; Vollebregt, van Dongen-Boomsma, Buitelaar, & Slaats-Willemse, 2013). The most optimistic outcome is of one single-blinded study, in which children with ADHD who received neurofeedback (n=18) improved more in attention as reported by parents and on neuropsychological measures of reaction time and accuracy than those receiving electromyography (EMG) biofeedback (n=17) (Bakhshayesh, Hansch, Wyschkon, Rezai, & Esser, 2011). The other

blinded studies failed to find larger reductions of ADHD-symptoms for neurofeedback than for placebo-neurofeedback in youngsters with ADHD (Arnold et al., 2012; Perreau-Linck et al., 2010; van Dongen-Boomsma et al., 2013). Note, however, that the sample sizes of these groups were relatively small, with included participants per condition for neurofeedback versus placebo-neurofeedback respectively, *n=4* versus *n=4* (Perreau-Linck et al., 2010), *n=25* versus *n=11* (Arnold et al., 2012) and *n=22* versus *n=19* (van Dongen-Boomsma et al., 2013). Notwithstanding the small sample sizes, these results indicate that the previously reported positive outcomes of the non-placebo controlled studies in ADHD were possibly the result of non-specific effects of the treatment such as motivation and expectations by parents and youngsters, the high-tech setting with a medical appearance and the large number of training sessions with a clinical expert.

There are fewer clinical effectiveness studies of neurofeedback in ASD than there are in ADHD. The most applied neurofeedback protocols in ASD consist of frequency training protocols (Holtmann et al., 2011) either similar to those applied in ADHD with inhibition of theta (4-7 Hz) and reinforcement of SMR (12-15 Hz) (Coben, Linden, & Myers, 2010) or suppression of the Mu rhythm (8-13Hz) (Coben et al., 2010; Holtmann et al., 2011). The review by Holtmann et al. (2011) states that although neurofeedback does not seem effective for ASD-features, it might be effective in reducing comorbid ADHD-symptomatology.

Overall, claims on the effectiveness of neurofeedback for ADHD symptoms range from 'efficacious and specific' (Arns, de Ridder, Strehl, Breteler, & Coenen, 2009) and 'probably effective' (Lofthouse et al., 2012; Moriyama et al., 2012), to not effective when examined within blinded designs (Sonuga-Barke et al., 2013). The range of effectiveness estimations is so broad because several methodological shortcomings have hampered many of the included studies: the majority of the studies were not randomized, sample sizes were small, and/or non-specific treatment effects were not controlled for. Therefore, more conservative estimations were reported recently (Gevensleben, Rothenberger, Moll, & Heinrich, 2012; Lofthouse et al., 2012; Loo & Makeig, 2012; Moriyama et al., 2012; Sonuga-Barke et al., 2013). All in all, previous shortcomings in study design and unknown (negative) side effects preclude strong conclusions. To address these shortcomings, more controlled research is necessary to see if there are specific patient groups that will profit from neurofeedback and if this depends on the kind of neurofeedback training protocol that is applied (Gevensleben et al., 2012; Lofthouse et al., 2012). In addition, research is needed to see whether neurofeedback can be of additional value to multimodal treatment protocols (Gevensleben et al., 2012). Furthermore, the value of neurofeedback in clinical practice needs to be invested, where more heterogeneous populations of youngsters with ADHD are seen. Accordingly, in order to resemble implementation in clinical practice, youngster with ADHD and comorbid disorders, such as ASD, who seek treatment for ADHD-symptoms should be included as well.

The aims of this thesis

This thesis has two aims. The first aim of this thesis is to explore psychophysiology in adolescents with ADHD and combined ASD+ADHD in relation to possible clinical implications. The second aim of this thesis is to investigate whether neurofeedback has additional value for TAU to improve behavior and neurocognitive functioning for adolescents with ADHD. Therefore, this thesis is divided into two parts. In the first part of this thesis, the overlap and differences in psychophysiological measures between adolescents with ADHD and adolescents with combined ASD+ADHD are explored (**Chapter 2-4**). In the second part of this thesis, the additional effects of neurofeedback for TAU for adolescents with ADHD are investigated (**Chapter 5-7**).

Study design and thesis layout

In order to investigate the additional value of neurofeedback to the current TAU, adolescents were recruited from three different mental healthcare centers for child and adolescent psychiatry in the south of the Netherlands: GGzE (Eindhoven), GGz Breburg (Breda and Tilburg) and the Reinier van Arkel group ('s-Hertogenbosch). Eligible participants were male adolescents with Dutch as their native language, ages 12 through 24 years old, with a clinical DSM-IV-TR primary diagnosis of ADHD and a full-scale total intelligence quotient (TIQ)>80. Adolescents diagnosed with ASD (including: Autism, Asperger disorder and PDD-NOS) with notification of clinical ADHD symptoms equal to a full ADHD diagnosis were also included. Exclusion criteria were neurological disorders, schizophrenia and other psychotic disorders.

At pre-intervention, participants were seen on three occasions for 1) the administration of behavioral questionnaires and neurocognitive tests, 2) the WAIS or WISC intelligence test, and 3) physiological measurements. In cases where participants were on medication, medication intake was also continued on the day of assessment. Interventions took place between December 2009 and July 2012. Duration of the intervention period was approximately 25 weeks. Interventions included either TAU as prescribed by the main therapist of the participating center for child and adolescent psychiatry or combined neurofeedback with TAU. Post-intervention assessment included behavioral questionnaires and neurocognitive tests. One year follow-up assessment included behavioral, neurocognitive and physiological measures.

The first part of this thesis explores potential physiological overlap and differences between adolescents with ADHD and combined ASD+ADHD, on and off stimulant medication, in cardiac reactivity **(Chapter 2)**, theta/ beta power spectra **(Chapter 3)** and event-related potentials **(Chapter 4)** at pre-intervention. Two diagnostic groups were compared: adolescent with ADHD versus combined ASD+ADHD. The first group consisted of adolescents with a clinical DSM-IV-TR primary diagnosis of ADHD, including: combined subtype, inattentive subtype, hyperactive /impulsive subtype. The second group consisted of adolescents with a primary diagnosis of ASD, including: Asperger disorder and Pervasive developmental disorder – not

otherwise specified (PDD-NOS). Adolescents with ASD also showed ADHD symptomatology equal to a full DSM-IV-TR ADHD diagnosis. To improve comparability on the investigated physiological measures, we also excluded adolescents with depression, attachment disorder, anxiety disorder, use of cannabis 24 hours prior to physiological assessment or medication use other than stimulant medication for these analyses.

In the second part of the thesis, the additional value of neurofeedback for TAU is investigated by comparisons of the pre-intervention and direct post-intervention assessments on behavior and side effects **(Chapter 5)** and neurocognitive functioning **(Chapter 6)** between adolescents with ADHD who received TAU and adolescents who received combined neurofeedback and TAU. Approximately half of the adolescents used stimulant medication and one third had an ASD diagnosis. Therefore, possible effects of stimulant medication use as well as having an ASD diagnosis were taken into account. Finally, additional effects of neurofeedback on behavior and neurocognitive functioning one-year after the intervention period are explored **(Chapter 7)**. At the end of this thesis, all findings are summarized and discussed **(Chapter 8)**.

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CHAPTER 2

Cardiac Reactivity and Stimulant Use in Adolescents with Autism Spectrum Disorders with Comorbid ADHD versus ADHD

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ABSTRACT

A large number of youngsters with autism spectrum disorders (ASD) display comorbid attention deficit/hyperactivity disorder (ADHD) symptoms. However, previous studies are not conclusive whether psychophysiological correlates, like cardiac reactivity, are different for ASD with comorbid ADHD (ASD+) compared to ADHD. Therefore, the current study investigated (dis)similarities in cardiac reactivity and attention task performance. In a clinical sample, adolescents diagnosed with ASD+ (n=20) versus ADHD (n=36) and stimulant medication use (56%) were compared during a baseline with eyes closed and task performance. Results for cardiac reactivity were similar for both diagnostic groups. Stimulant-medicated adolescents showed decreased adaptation of LF/HF ratio and faster reaction times than stimulant-free adolescents. The current study underlines the psychophysiological overlap of ADHD symptoms in adolescents with ASD+ and adolescents with ADHD.

INTRODUCTION

Adolescents with autism spectrum disorders (ASD) show severe and persistent problems with social interaction, communication and/or display stereotyped behavior, interests and activities (American Psychiatric Association, 2000). More than half of youngsters with ASD also experience comorbid symptoms of Attention Deficit Hyperactivity Disorder (ADHD) at a clinical level (Gadow, DeVincent, & Pomeroy, 2006; Holtmann, Bolte, & Poustka, 2007). However, in the DSM-IV-TR (American Psychiatric Association, 2000) ADHD was excluded as a diagnosis in ASD. In order to prevent that children with ASD and ADHD symptoms are excluded from potentially beneficial treatment for ADHD, the DSM-V taskforce has removed ASD from the exclusion criteria of ADHD (American Psychiatric Association, 2012). Nevertheless, previous studies are not conclusive whether psychophysiological correlates are different for ADHD in ASD compared to ADHD (American Psychiatric Association, 2012). Consequently, it is uncertain whether treatment for ADHD, like stimulant medication, work equally well in children with ASD and comorbid ADHD (ASD+) as in children with ADHD. Stimulant medication showed improved attention and diminished hyperactivity and impulsivity symptoms in children with ADHD (Gorman, Klorman, Thatcher, & Borgstedt, 2006). ADHD symptom reduction by stimulant medication seems dose dependent, with better responses in children with predominant hyperactive/impulsivity (HI) symptoms to higher doses and in children with predominant inattentive (I) symptoms to lower doses (Barkley, DuPaul, & McMurray, 1991; Stein et al., 2003). Comparison of two large corporate studies that investigated reactions to stimulant medication in children with ADHD (Greenhill et al., 2001) and children with ASD+ (Research Units on Pediatric Psychopharmacology (RUPP) Autism Network, 2005) indicates that there are differences for the two groups. For example, where stimulant medication improves behavior in nearly three-quarters of children with ADHD (Greenhill et al., 2001), this is only 49 percent in ASD+ (RUPP, 2005). Moreover, adverse effects, such as irritability, decreased appetite, and difficulty falling asleep are more often seen in stimulant medicated ASD+ patients. In fact, 18 percent of the children with ASD+ had to stop stimulant medication because of adverse effects (RUPP, 2005), compared to only 1.5 percent in children with ADHD (Greenhill et al., 2001). The lower response rate and higher prevalence of adverse effects reported for stimulant medication in the ASD+ group may reflect differential psychophysiological mechanisms underlying ADHD symptoms in ADHD versus ASD+.

Cardiac reactivity has been related to different psychological processes as attention, behavioral inhibition and social engagement (Porges, 2007) and consequently to key symptoms of both ADHD and ASD. To date, several studies indeed differentiate in cardiac reactivity for youngsters with ASD compared to typically developing (TD) youngsters (Althaus, Mulder, Mulder, Aarnoudse, & Minderaa, 1999; Van Hecke et al., 2009) and in youngsters with ADHD compared to TD youngsters (Borger & van der Meere, 2000; Borger et al., 1999; Luman, Oosterlaan, Hyde, van Meel, & Sergeant, 2007). However, cardiac reactivity has not been compared between ASD+ and ADHD. Therefore, the aim of

this study is to explore (dis)similarities in cardiac reactivity and attention task performance in stimulant-medicated and stimulant-free adolescents, diagnosed with ASD+ versus ADHD.

In the last two decades, cardiac activity in heart rate (HR) and heart rate variability (HRV) has been increasingly studied in relation to behavior and cognition. HRV represents the variation of beat-to-beat intervals in an electrocardiogram (ECG) and reflects the interchange between sympathetic and parasympathetic impact on the cardiac pacemaker. Task effort and stress have been shown to induce an adaptation of cardiac activity (Jorna, 1992). Previous studies have found mixed results for cardiac activity during resting baseline. Compared to TD children, children with ASD showed higher heart rates and less HRV in rest conditions, that indicates increased sympathetic activation in children with ASD (Bal et al., 2010; Daluwatte et al., 2012; Van Hecke et al., 2009). Other studies, however, failed to find any differences during rest conditions between TD children and adolescents and those with ASD(+) (Althaus et al., 1999; Toichi & Kamio, 2003).

Whereas increased sympathetic activation is supposed in ASD (Bal et al., 2010; Daluwatte et al., 2012; Van Hecke et al., 2009), indications for increased parasympathetic activation were found in stimulant-free children with ADHD across different studies (Borger & van der Meere, 2000; Borger et al., 1999; Negrao, Bipath, van der Westhuizen, & Viljoen, 2011). More specific, increased HRV was found during attention task performance in stimulant-free children with ADHD compared to TD children (Borger & van der Meere, 2000; Borger et al., 1999). In addition, increased HRV and lower HR during resting baseline were found for stimulant-free children with ADHD compared to TD children (Negrao et al., 2011). However, HRV and HR were similar for stimulant-medicated children with ADHD and TD children (Negrao et al., 2011). Accordingly, Negrao et al. (2011) postulated the assumption that stimulant medication decreases the parasympathetic activation and thereby normalizes the autonomic balance. This idea is in line with the majority of research that shows elevation of HR due to stimulant medication (Hammerness, Perrin, Shelley-Abrahamson, & Wilens, 2011). Nevertheless, similar to the pattern observed during rest conditions in children with ASD, other cardiac studies in children with ADHD failed to find differences in cardiac activity between stimulant-free children with ADHD and TD children (Beauchaine, Katkin, Strassberg, & Snarr, 2001; Jennings, van der Molen, Pelham, Debski, & Hoza, 1997). In contrast, there are even studies that indicate elevated HR and decreased parasympathetic activation in children with ADHD and that medication reduces HR and increases parasympathetic activation (Buchhorn et al., 2012; Rash & Aguirre-Camacho, 2012). However, Beauchaine et al. (2001), showed that only children with ADHD and comorbid conduct disorder show significant decreased parasympathetic activation compared to children with ADHD and TD children. This assumes that the comorbid symptoms of conduct disorder are related to decreased parasympathetic activation rather than to ADHD symptoms.

Findings have been more consistent with respect to differential patterns of cardiac adaptation to tasks. In the early nineties, Porges (1995, 2007) described the common presentation of a decrease in HRV in healthy subjects when they perform an attention-demanding task compared to a resting baseline condition. Moreover, a positive relation was observed for cardiac adaption and task

performance (Porges, 2007). In line with this theory, task-related cardiac adaptation with decreased HRV was observed in TD children and stimulant-free children with ADHD (Borger & van der Meere, 2000; Jennings et al., 1997; Luman et al., 2007; Negrao et al., 2011). However, task-related cardiac adaptation was not observed in stimulant-medicated children with ADHD (Negrao et al., 2011). Likewise, children and young adults with ASD also seem to show less task-related cardiac adaptation than TD controls (Althaus et al., 1999; Toichi & Kamio, 2003). Therefore, it seems that ASD and stimulant medication use are both related to a reduced task-related cardiac adaptation.

Attention symptoms that occur in youngsters with ADHD or ASD may result in diminished attention task performance. Several studies showed that children with ADHD display longer reaction times and more variability in reaction times than TD children (Banaschewski et al., 2003; Borger & van der Meere, 2000; Groen et al., 2008; Jennings et al., 1997). The study of Althaus et al. (1999) also presented longer reaction times in youngsters with ASD and ASD+ compared to TD controls. However, a study by Groen et al. (2008) did not find such differences in reaction times for ASD compared to TD children. More specifically, the study showed that only stimulant-free children with ADHD display more variability in reaction times than stimulant-medicated children with ADHD, children with ASD and TD children. Results with regard to accuracy are ambiguous. For example, Groen et al. (2008) did show that children with ADHD or ASD made more errors than TD children during attention task performance. Whereas, Althaus et al. (1999) showed that children with ASD+, but not children with ASD, made more errors than TD children. In addition, some studies did not even find significant differences between ADHD and TD children (Banaschewski et al., 2003; Borger & van der Meere, 2000). Group differences of accuracy in the studies, might have been suppressed by a ceiling effect due to the low amount of errors during sustained attention tasks.

To summarize, ADHD symptoms are present in a large number of patients diagnosed with ASD. At this time, it is not clear whether psychophysiological characteristics are similar in ASD+ patients and ADHD patients. Therefore, the aim of this study is to explore (dis)similarities in cardiac reactivity and attention task performance in stimulant-medicated and stimulant-free adolescents, diagnosed with ASD+ versus ADHD.

It was expected that psychophysiological measures are dependent on diagnostic group (ASD+ versus ADHD, stimulant medication use, stimulant-free versus stimulant-medicated adolescents) and the interaction of diagnostic group and stimulant medication use. More specifically, with respect to cardiac reactivity it was expected that: (1) ASD+ adolescents display higher HR, less HRV and less task related cardiac adaptation than ADHD adolescents, (2) stimulant-medicated adolescents will display higher HR, less HRV and less task-related cardiac adaptation than the stimulant-free adolescents, and (3) the interaction of cardiac activity and stimulant medication use is smaller in the ASD+ group than in the ADHD group. With respect to cognitive performance on the attention task it was expected that, stimulant-medicated adolescents would show enhanced performance compared to stimulant-free adolescents in both diagnostic groups.

METHOD

Participants

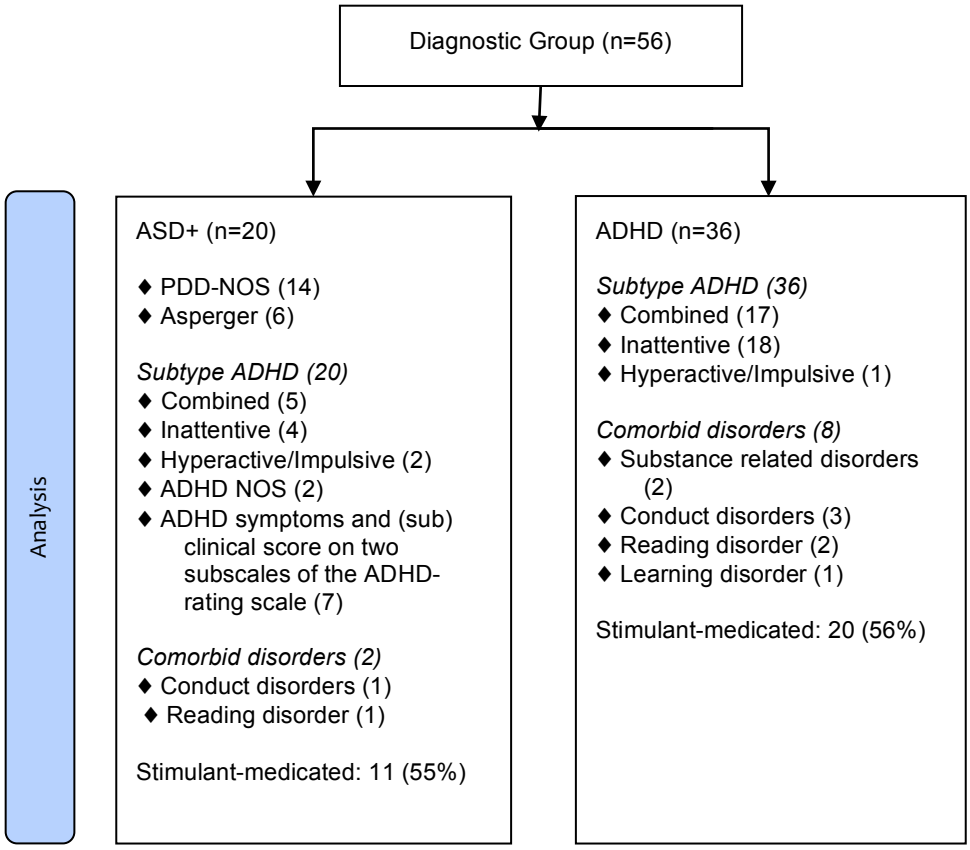
Eligible participants were native Dutch speaking male adolescents, between 12 and 24 years old, a clinical DSM-IV-TR primary diagnosis of ADHD or ASD (including: PDD-NOS and Asperger disorder) with notification of clinical ADHD, symptoms equal to a full ADHD diagnosis, a full-scale total intelligence quotient (TIQ) > 80 on the Wechsler Intelligence Scale for Children (WISC-III) or the Wechsler Adult Intelligence Scale (WAIS-III) (Wechsler, 1991, 1997). ADHD symptoms were verified by a DSM-IV based Dutch semi-structured ADHD interview for adults (Kooij, 2002) and the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998; Sheehan et al., 1997). Exclusion criteria were neurological disorders, schizophrenia or another psychotic disorder, depression, attachment disorder or anxiety disorder. Presence of other comorbid disorders was allowed.

Stimulant medication use was allowed. Adherence to prescribed stimulant medication was verified by asking the participants whether they took their medication on the day of assessment. Participants were excluded for analysis if they forgot to take the prescribed medication on the day of assessment, used antidepressant medication, used atomexetine, and/or used recreational drugs in the last 24 hours prior to assessment.

Fifty-six participants were divided in two diagnostic groups. These groups are presented in Figure 1. The final group characteristics are listed in Table 1. The first group consisted of 20 adolescents with a primary DSM-IV-TR diagnosis of ASD with ADHD symptoms (ASD+ group). Although the diagnoses ASD and ADHD are mutually exclusive according to the DSM-IV-TR, 13 (65%) participants received a secondary diagnosis of ADHD. In addition to the inclusion criteria, the seven (35%) participants who did not have a secondary ADHD diagnosis, had to score (sub)clinical on two subscales of the ADHD-rating scale (See further description below; Kooij et al., 2008; Kooij et al., 2005). The second group consisted of 36 adolescents with a primary DSM-IV-TR diagnosis of ADHD (ADHD group).

In total 31 (55%) participants used stimulant medication. In the ASD+ group, 11 (55%) used stimulant medication: one used immediate release methylphenidate, 10 used sustained release methylphenidate. Two adolescents in the ASD+ group used low doses (0.5 mg and 1.5 mg per day) of antipsychotic medication (Risperdal®) in addition to their stimulant medication. Because of the low doses, possible impact on the cardiac measures was considered minimal. In the ADHD group, 20 (56%) used stimulant medication: six used immediate release methylphenidate, 14 used sustained release methylphenidate.

Figure 1. *Diagram with diagnostic characteristics of the groups.*



Measures

Group characteristics

ASD symptoms were screened with the Autism-Spectrum Quotient (AQ)-adolescent version, which is a questionnaire for individuals with normal intelligence (Baron-Cohen, Hoekstra, Knickmeyer, & Wheelwright, 2006; Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001). The AQ-adolescent version is a parent report and was completed by parents or significant others. Dichotomous scoring was applied and all item scores were summed. In the AQ validity study of Baron-Cohen et al. (2006) 87% of the male ASD adolescents seem to score 30 points or more on the AQ-adolescent versus none of the TD adolescents. Therefore, the advised critical minimum to screen for ASD is 30 points or more (Baron-Cohen et al., 2006).

The ADHD-rating scale is a DSM-IV-based self-report for adults (Kooij et al., 2008; Kooij et al., 2005) We used the adapted form (DuPaul et al., 1998) which contains 23 items rated on a 4-point scale ranging from 'rarely or never' to 'very often'. Items are completed for occurrence over the last six months and childhood. Participants were instructed to consider the 23 items over childhood for the primary school period. Each 23-item list is divided in two nine-item subscales: inattention and hyperactivity/ impulsivity (HI) (Kooij et al., 2008; Kooij et al., 2005).

The Child Behavior Checklist (CBCL) and the Youth Self Report (YSR) (Achenbach, 1991) are questionnaires that cover behavioral and emotional problems in children and adolescents up to 18 years old. In this study, the subscale attention problems, the two broadband scales internalizing and

externalizing problems and the global scale total problems were used. The CBCL and YSR were administered to all participants from 12 to 24 years old, because most of the participants older than 18 years old were still in school and living with their parents.

Corresponding with the age of the participants, the Wechsler Intelligence Scale for Children (WISC-III) or the Wechsler Adult Intelligence Scale (WAIS-III) was administered (Wechsler, 1991, 1997). Full-scale total intelligence quotient (TIQ), verbal intelligence quotient (VIQ), and performance intelligence quotient (PIQ) were calculated. When available, WAIS or WISC scores from less than a year old of the participant were obtained from the mental healthcare institution.

Physiological measures

The electrocardiogram (ECG) was recorded between 10 and 11 o'clock in the morning. If applicable, stimulant medication was taken during breakfast before the measurement. No caffeine or nicotine intake was allowed two hours prior to physiological measurement. The ECG recording was part of an EEG-recording in combination with a subset of the brain resource company (BRC, Ultimo, Australia) test battery. This included a baseline condition in which the adolescent had to sit quietly with closed eyes for two minutes. Subsequently, they performed the task condition that consisted of an auditory oddball task lasting six minutes.

Electrocardiogram (ECG) was recorded with two Ag/AgCl electrodes attached between the collarbones over the jugular notch of the sternum and at the fifth intercostal space at the left anterior axillary line (V5). A NuAmps amplifier amplified the signals and Neuroscan software recorded the signals with a sampling rate of 500 Hz. The occurrence of R-peaks was detected automatically by using BioSig software (Schlögl, 2009). The location of R-peaks was visually checked and manually adapted if necessary. Thereafter, the ECG data was further automatically analyzed by Kubios software (Niskanen, Tarvainen, Ranta-Aho, & Karjalainen, 2004; Tarvainen & Niskanen, 2008).

The following time domain measures of HRV were taken into account: (1) Mean time in ms between two successive R-peaks (RR), (2) the standard deviation of RR (RR SD), (3) mean heart rate (HR) in beats per minute (bpm), (4) the standard deviation of HR (HR SD), and (5) the root mean square of differences of successive RR intervals (RMSSD) as an estimate of short-term components of HRV (Malliani, Pagani, Lombardi, & Cerutti, 1991; Task Force, 1996).

The other measurements are in the frequency domain. The power spectral density (PSD) was calculated from the RR series parametrically based on an autoregressive (AR) model of order 16. For the present study, the following measures were further analyzed: (1) low frequency power (LF, 0.04-0.15 Hz), (2) high frequency power (HF, 0.15-0.4 Hz), and (3) the low frequency-high frequency ratio (LFHF). Because of the short analysis period for the baseline measure (2 min), it was not possible to interpret the very low frequency band (VLF, 0.0-0.04 Hz; Task Force 1996). HF and LF power can be seen as an indicator of parasympathetic modulation, and the LFHF ratio is thought to reflect autonomic cardiovascular modulation (Reyes del Paso, Langewitz, Mulder, van Roon, & Duschek, 2013).

Auditory oddball task

The auditory oddball task is an attention test in which relevant stimuli need to be processed and irrelevant stimuli need to be ignored. In this task, every second a tone of 75 dB (A) for the duration of 50 ms is presented binaurally. Low tones of 500 Hz were presented interchanged with infrequent high tones of 1000 Hz in quasi-random order. Rise and fall times of all the tones was 5 ms. The adolescents were asked to press the answer box with both their index fingers as fast as they could when they heard the high 1000 Hz tone. In total, the low tones were presented 280 times and the high tones 60 times in 6 minutes. Response measures used were: mean reaction time to the odd high tones, standard deviation of the mean reaction time, number of incorrectly ignored high tone stimuli (omission errors), number of incorrectly not ignored low tone stimuli (inhibition errors).

Procedure

Participants were recruited for an intervention study for adolescents with clinical ADHD symptoms. Prior the start of the study approval was obtained from the medical ethics committee for mental health institutions in the Netherlands (Ref. no: NL 24776.097.08 CCMO). The study took place in three large secondary care centers of child and adolescent psychiatry (GGzE, GGz Breburg, Reinier van Arkel group) in the Southern part of the Netherlands. After the study was explained (verbally and in writing), written informed consent was obtained from each participant. For those younger than 18, parents also completed a written informed consent.

DSM classification and information about medication use were obtained from the clinical professionals of the corresponding center of child and adolescent psychiatry. Complete DSM classification was retrieved from the electronic patient record. Medication use was monitored through an intervention questionnaire based on the "Dutch national basic ADHD program for children and adolescents" (Vink & Van Wamel, 2007). Stimulant medication use included immediate release methylphenidate and sustained release methylphenidate (Concerta®, Equasym®, Medikinet®).

Participants were seen on three occasions. During the first appointment inclusion criteria were checked using an interview and behavioral questionnaires. During the second appointment, intellectual functioning was estimated, using the WAIS or WISC (Wechsler, 1991, 1997). Finally, during the third appointment, physiological measurements were noted. For one participant, the auditory oddball stimuli responses were not recorded correctly during physiological measurement and data were irretrievably lost. Eleven participants used marihuana in the 24-hours prior to physiological assessment, two participants used atomexetine, one participant used citalopram and two other participants who normally took prescribed stimulant medication but not on the day of physiological assessment. These 17 cases were excluded from analysis.

Parents or significant others received the CBCL and AQ-adolescent by mail, with the request to complete and return them on the assessment day or by mail. For two participants, AQ-adolescent and CBCL-scores were not retrieved and for three other cases the AQ-adolescent was not completed. These five cases were also excluded from analysis.

Data Analyses

All analyses were performed using SPSS version 19.0. There were violations of normality for the cardiac measures and reaction time measures; these were converted with a log10 function to obtain more normally distributed values. After the log10 transformations, assumptions of normality for cardiac measures were not violated.

Differences in group characteristics were analyzed with a one-way ANOVA. Separate Generalized Linear Model (GLM) ANCOVA's were conducted for each cardiac variable (time and frequency domain) during baseline and oddball task performance with diagnostic group (ASD+ or ADHD) and stimulant use (stimulant-medicated and stimulant-free) as within subject factor and the covariates age and PIQ. Stimuli response variables of the oddball task were analyzed with only age as the covariate.

Post hoc analyses were performed with redistribution of the participants. The first redistribution was based on the critical minimum of 30 points on the AQ-adolescent as indicated by Baron-Cohen et al. (2006), to compare participants with a score less than 30 points to participants with a score of 30 points or higher. The second redistribution was made to compare only the participants within the ASD+ diagnostic group *and* an AQ-adolescent score above 30 to the participants within the ADHD diagnostic group *and* an AQ-adolescent score less than 30. This means that participants diagnosed with ASD+ with AQ-adolescents scores under the critical minimum were excluded as well as participants diagnosed with ADHD with AQ-adolescents scores above the critical minimum.

Task-related cardiac adaptation was investigated using a Generalized Linear Model (GLM) with between and within-subjects factors. The analysis was applied to all the cardiac measures separately with diagnostic group and stimulant use as between subject factors and task (e.g., between baseline eyes closed condition and auditory oddball task) as within subjects factor. The full factorial models were tested. Within-subjects effects of the cardiac measures for task from the GLM were used to assess the validity of the cardiac measures. All task-related cardiac adaptation effects were evaluated using multivariate test criteria, which is known to be robust in case of violations of sphericity (Vasey & Thayer, 1987).

The adjusted least significant difference (LSD) and 95% confidence interval [95% CI] for diagnostic group (ADHD, ASD+ADHD), medication use (stimulant-free, stimulant-medicated) and task (baseline, task) were noted. Values of $p<.05$ were considered statistically significant. Because of the exploratory nature of the current study, no alpha correction for multiple testing has been applied. Effect sizes are expressed in percentage of explained variance in partial $\eta 2$ (η_p^2).

RESULTS

Group Characteristics

Group characteristics are summarized in Table 1. There were no differences for diagnostic group characteristics between the ASD+ group and the ADHD group in age (M=15.45, SD=3.02 years) [F

(1, 54)=.08, p>.05] and stimulant medication use [χ^2(1, 54)=.00, p>.05]. In addition, the mean prescribed doses in mg for the stimulant-medicated adolescents was similar in the ASD+ group (N=11, M=35.27, SD=17.35, 95%-CI =25.84, 44.71) as in the ADHD group (N=20, M=34.45, SD=14.11, 95%-CI= 27.45, 41.45) [F(1, 29)=.02, p>.05, ηp2=.00]. However, there was a trend for stimulant-free adolescents (M=16.32, SD=3.24 years) to be older than the stimulant-medicated adolescents (M = 14.74, SD = 2.67 years) [F(1,54)=4.0, p=.05]. Stimulant-free and stimulant-medicated adolescents did not differ significantly on other group characteristics.

The diagnostic groups did not differ on scores of Global Assessment of Functioning. ADHD symptoms as measured by MINI scores for inattention and hyperactivity/impulsivity (H/I), the ADHD-rating scale for inattention and H/I over the last six months as well as the childhood inattention and H/I were similar for both diagnostic groups.

Table 1. Group Characteristics[1]

	TOTAL	ASD+		ADHD		F	η_p^2
	N=56	N=20		N=36			
	Mean (SD)	Mean (SD)	[95% CI]	Mean (SD)	[95% CI]		
Age in Years	15.45 (3.02)	15.60 (2.62)	[14.37, 16.83]	15.36 (3.24)	[14.26, 17.09]	.08	.00
GAF-score	55.25 (6.39)	54.50 (6.10)	[51.65, 57.35]	55.67 (6.59)	[53.44, 57.90]	.42	.01
AQ-adolescent version[2]	25.62 (7.83)	32.45 (5.36)	[29.94, 34.96]	21.82 (6.25)	[19.70, 23.94]	40.96***	.43
ADHD-rating scale[3]							
Inattention	4.84 (2.34)	4.90 (2.25)	[3.85, 5.95]	4.81 (2.42)	[3.99, 5.63]	.02	.00
H/I	3.32 (1.93)	3.70 (2.06)	[2.74, 4.66]	3.11 (1.85)	[2.49, 3.74]	1.21	.02
Child Inattention	6.04 (2.62)	5.65 (2.83)	[4.32, 6.98]	6.25 (2.51)	[5.40, 7.10]	.67	.01
Child H/I	4.93 (2.77)	4.20 (2.75)	[2.92, 5.48]	5.33 (2.74)	[4.41, 6.26]	2.20	.04
MINI ADHD Inattention	5.39 (2.49)	5.00 (2.53)	[3.81, 6.19]	5.61 (2.48)	[4.77, 6.45]	.77	.01
MINI ADHD H/I	3.73 (2.39)	3.60 (2.39)	[2.48, 4.72]	3.81 (2.41)	[2.99, 4.62]	.09	.00
CBCL Total Problems	61.82 (28.28)	72.95 (28.27)	[59.72, 86.18]	55.64 (26.70)	[46.61, 64.67]	5.19*	.09
Internalizing Problems	14.02 (9.44)	17.55 (10.37)	[12.69, 22.41]	12.06 (8.40)	[9.21, 14.90]	4.64*	.08
Externalizing Problems	18.55 (11.48)	21.80 (11.06)	[16.62, 26.98]	16.75 (11.46)	[12.87, 20.63]	2.56	.05
Attention Problems	11.88 (3.41)	12.80 (3.62)	[11.11, 14.49]	11.36 (3.22)	[10.27, 12.45]	2.35	.04
YSR Total Problems	47.07 (20.01)	54.30 (21.43)	[44.27, 64.33]	43.06 (18.26)	[36.88, 49.23]	4.31*	.07
Internalizing Problems	8.98 (5.82)	10.90 (6.09)	[8.05, 13.75]	7.92 (5.46)	[6.07, 9.76]	3.53	.06
Externalizing Problems	15.32 (9.55)	17.85 (9.89)	[13.22, 22.48]	13.92 (9.19)	[10.81, 17.03]	2.23	.04
Attention Problems	9.50 (3.10)	8.85 (3.59)	[7.17, 10.53]	9.86 (2.79)	[8.92, 10.80]	1.37	.02
TIQ	101.39(10.87)	104.90(11.60)	[99.47, 110.33]	99.44 (10.09)	[96.03, 102.86]	3.38	.06
VIQ	102.55(11.39)	106.75(12.07)	[101.10, 112.4]	100.22(10.45)	[96.69, 103.76]	4.49*	.08
PIQ	100.54(13.12)	102.45(11.80)	[96.93, 107.97]	99.47 (13.85)	[94.79, 104.16]	.66	.01

Note: [1]data are means (SD); Df (1,54); *p<.05, **p<.01, ***p<.001; [2]Autism Spectrum Quotient (AQ)-adolescent version is a parent report; [3]the ADHD-rating subscales are self-reported over the last six months, the child subscales are retrospective self-reported for the primary school period.

The AQ-adolescent confirmed that the ASD+ group exhibited more autism symptoms than the ADHD group [$F(1,54) = 40.96$, $p < .001$] with a range of 23-42 for the ASD+ group and 10-36 for the ADHD group. For the ASD+ group, parents reported on the CBCL more total behavioral problems, specifically more internalizing problems. On the YSR the adolescents in the ASD+ group reported also more total problems, with a trend for internalizing problems [$F(1,54) = 3.53$, $p = .07$]. Externalizing problems and attention problems were similar for both groups on the CBCL and the YSR. The ASD+ group had a higher VIQ compared than the ADHD group and there was a trend for TIQ to be higher [$F(1,54) = 3.37$, $p = .07$]. PIQ scores were similar for both groups.

Physiological Measures

Cardiac activity

Cardiac measures are summarized in Table 2. Raw HR (bpm) data is listed italicized on the first line of both conditions (baseline and task). All other cardiac measures are presented with log-transformed data. Untransformed HR was M = 74, SD = 12 bpm during baseline and M=77, SD=14 bpm during task performance (see also Table 3).

The cardiac measures showed no effects of diagnostic group during baseline or task performance. LFHF ratio differed between stimulant-medicated and stimulant-free adolescents: stimulant-medicated adolescents showed relative higher LF power to lower HF power and the stimulant-free adolescents relative higher HF power to lower LF power [$F(5,50) = 6,46$, $p < .05$, $\eta_p^2 = .11$]. There was no differentiation between stimulant-medicated and stimulant-free adolescents on the other cardiac measures. Furthermore, there was no interaction of diagnostic group and stimulant medication use on any of the cardiac measures.

The older adolescents showed less HRV during baseline; older adolescents showed decreased HR SD, HR and increased RR intervals compared to younger adolescents. In addition, older adolescents showed decreased HF power and increased LFHF ratio than younger adolescents. During task performance age revealed a decrease in HR SD and an increase in LFHF ratio. The other cardiac measures revealed no effect of age during task.

PIQ is negative related to RR SD and LF power during baseline and task performance. Adolescents with higher PIQ scores show decreased RR SD and LF power, compared to adolescents with lower PIQ scores.

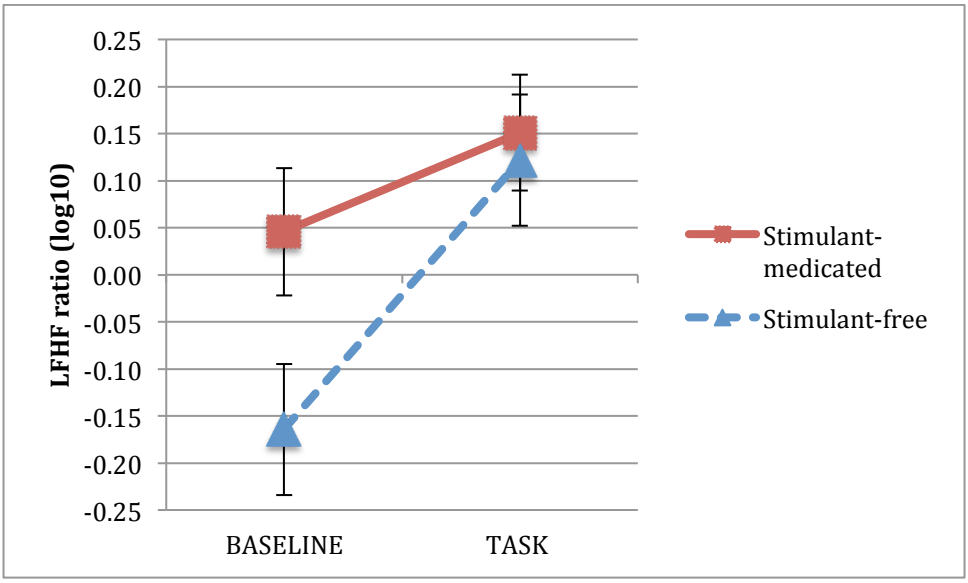
Post hoc analyses with redistribution of the diagnostic groups based on the AQ-adolescent critical minimum (Baron-Cohen et al., 2006) revealed no differences in cardiac measures between the group with a score less than 30 points (n=39) and the group with a score 30 points or higher (n=17) and no interactions between group and stimulant medication use. Furthermore, comparing the adolescents with ASD+ and an AQ-adolescents score above the critical minimum of 30 points (n=13) to the adolescents with ADHD and an AQ-adolescent score less than 30 points (n=32) showed no differences in cardiac measures and no interactions between group and stimulant medication use.

Task related cardiac adaptation

Cardiac adaptation measures are summarized in Table 3. Task related cardiac adaptation for the total group was observed as expected, with a decrease in mean RR, an increase HR and HR SD, a decrease in high frequency power (HF), and increase in LFHF ratio between baseline condition and auditory oddball task performance.

There was an interaction between task related cardiac adaptation and stimulant medication for LFHF ratio [F (3, 52) = 4.75, p<.05, η_p^2= .08]. The stimulant-free group showed a greater task related increase in LFHF ratio (baseline M=-.16, SD=.35 and task M=.12, SD= .35), while a more modest increase is seen for the stimulant-medicated group (baseline M=.05, SD= .38 and task M=.15, SD=.34) (see Figure 2). Note that even though equality of error variances was not violated, the standard deviations for the LFHF ratio were relatively high. The other measures revealed no interactions of stimulant medication use and task-related cardiac adaptation. Cardiac adaptation was similar for the diagnostic groups (ASD+ or ADHD) on all the cardiac measures. Furthermore, no interactions between stimulant medication and diagnostic group were found for task-related cardiac adaptation.

Figure 2. *Interaction of cardiac adaptation and stimulant medication use for LFHF ratio*



Note: mean log 10 LFHF ratios with standard error bars are displayed during baseline and task for the stimulant-free and the stimulant-medicated group. The interaction between stimulant medication use and cardiac adaptation for LFHF ratio was significant [F (3, 52) = 4.75, p<.05, ηp2= .08].

Auditory Oddball Task

The adolescents on stimulant medication responded faster and with less variability than stimulant-free adolescents (see Table 4). Stimulant medication appeared unrelated to inhibition or omission errors. Diagnostic group (ASD+ or ADHD) or interaction between diagnostic group and medication had no effect on performance results.

Table 2. GLM ANCOVA of cardiac measures during closed eyes baseline and task performance by diagnostic group and medication use, with age and PIQ as covariate[1]

	ASD+ (n=20) Mean (SD)	ADHD (n=36) Mean (SD)	Adjusted difference [95% CI] at GROUP	Stim-free (n=25) Mean (SD)	Stim-med (n=31) Mean (SD)	Adjusted difference [95% CI] at STIM	AGE F	AGE η_p^2	PIQ F	PIQ η_p^2	GROUP F	GROUP η_p^2	MED F	MED η_p^2	GROUP*MED F	GROUP*MED η_p^2
BASELINE																
HR (bpm)[2]	*75 (10)*	*74 (14)*		*70 (10)*	*78 (13)*											
HR	1.87 (.06)	1.86 (.08)	-.01 [-.05, .03]	1.84 (.06)	1.89 (.07)	-.03 [-.07, 01]	4.68*	.09	1.05	.02	.34	.01	2.32	.04	.19	.00
HR SD	.76 (.13)	.77 (.19)	.01 [-.08, .09]	.73 (.20)	.79 (.14)	-.03 [-.12, .05]	15.56***	.24	2.61	.05	.02	.00	.60	.01	.54	.01
RR mean	2.91 (.06)	2.92 (.08)	.01 [-.03, .05]	2.94 (.06)	2.90 (.07)	.03 [-.01, .07]	4.20*	.08	1.23	.02	.40	.01	2.44	.05	.24	.00
RR SD	1.79 (.14)	1.82 (.19)	.02 [-.07, .12]	1.83 (.19)	1.80 (.16)	.02 [-.08, .12]	3.21	.06	5.18*	.09	.24	.00	.24	.00	.86	.02
RMSSD	1.67 (.17)	1.73 (.29)	.06 [-.08, 20]	1.77 (.26)	1.66 (.24)	.11 [-.03, .26]	3.00	.06	1.94	.04	.76	.02	2.54	.04	.79	.02
LF power	3.02 (.39)	3.06 (.39)	.02 [-.20, .24]	3.01 (.38)	3.08 (.40)	-.09 [-.32, 14]	1.14	.02	4.30*	.08	.04	.00	.63	.01	.85	.02
HF power	3.03 (.35)	3.13 (.53)	.08 [-.18, .33]	3.17 (.50)	3.03 (.45)	.18 [-.09, .45]	7.27**	.13	1.97	.04	.37	.01	1.86	.04	.79	.02
LFHF ratio	-.01 (.40)	-.07 (.36)	-.06 [-.26, .15]	-.16 (.35)	.05 (.38)	-.27 [-.49, -.06]	4.91*	.09	.21	.00	.30	.01	6.46*	.11	.02	.00
TASK																
HR (bpm)[2]	*77 (11)*	*76 (16)*		*72 (10)*	*80 (17)*											
HR	1.88 (.06)	1.87 (.08)	-.00 [-.05, .04]	1.85 (.06)	1.90 (.09)	-.03 [-,07, .02]	2.84	.05	1.63	.03	.05	.00	1.66	.03	.09	.00
HR SD	.78 (.14)	.82 (.17)	.03 [-.05, .11]	.79 (.18)	.81 (.14)	-.01 [-.10, .08]	7.60**	.13	2.95	.06	.53	.01	.05	.00	.93	.02
RR mean	2.90 (.06)	2.91 (.09)	.01 [-.04, .05]	2.93 (.06)	2.89 (.09)	.03 [-.02, .07]	2.54	.05	1.79	.04	.07	.00	1.79	.04	.12	.00
RR SD	1.79 (.17)	1.84 (.20)	.04 [-.06, 15]	1.86 (.21)	1.80 (.17)	.04 [-.07, 15]	.69	.01	5.49*	.10	.67	.01	.64	.01	.97	.02
RMSSD	1.63 (.27)	1.71 (.32)	.07 [-.09, .23]	1.75 (.30)	1.63 (.27)	.11 [-.06, .27]	1.34	.02	2.74	.05	.74	.01	1.69	.03	.56	.01
LF power	3.12 (.35)	3.12 (.41)	-.02 [-.24, .20]	3.18 (.36)	3.07 (.42)	.05 [-.17, .28]	.10	.00	5.49*	.10	.03	.00	.22	.00	.95	.02
HF power	2.88 (.42)	3.04 (.59)	.13 [-.16, 43]	3.05 (.56)	2.92 (.53)	.14 [-17, .45]	2.90	.06	2.70	.05	.82	.02	.84	.02	.49	.01
LFHF ratio	.24 (.31)	.08 (.35)	-.15 [-.34, .04]	.12 (.35)	.15 (.34)	-.09 [-.29, .11]	5.35*	.10	.01	.00	2.61	.05	.81	.02	.00	.00

Note:[1]log10 scales are applied to all cardiac measures, *p<.05, **p<.01, ***p<.001; Df (5,50); RR SD is SDNN; Adjusted difference [95% CI] at Group (ADHD minus ASD+) at STIM (stimulant-free minus stimulant-medicated); [2]untransformed HR in beats per minute (bpm).

Table 3. Task related cardiac adaptation[1]

	BASELINE	TASK	Adjusted difference	TASK		TASK*GROUP		TASK*STIM		TASK*GROUP*STIM	
	Mean (sd)	Mean (sd)	[95% CI] at TASK	F	η_p^2	F	η_p^2	F	η_p^2	F	η_p^2
HR (bpm)[2]	*74 (12)*	*77 (14)*									
Heart Rate	1.87 (.07)	1.88 (.08)	-.01 [-.02, -.00]	7.95**	.13	.53	.01	.05	.00	.19	.00
Heart Rate SD	.77 (.17)	.80 (.16)	-.04 [-.06, -.00]	5.45*	.10	.56	.01	1.72	.03	.03	.00
RR mean	2.92 (.07)	2.91 (.08)	.01 [.00, .02]	7.48**	.13	.55	.01	.02	.00	.20	.00
RR SD	1.81 (.17)	1.82 (.19)	-.01 [-.04, .02]	.58	.01	.40	.01	1.30	.02	.00	.00
RMSSD	1.71 (.25)	1.68 (.29)	.03 [-.00, .06]	3.23	.06	.12	.00	.05	.00	.13	.00
LF power	3.04 (.39)	3.12 (.39)	-.09 [-.18, 00]	3.90	.07	.21	.00	3.80	.07	.00	.00
HF power	3.10 (.36)	2.98 (.54)	.12 [.06, .19]	15.86***	.23	.90	.02	.00	.00	.21	.00
LFHF ratio	-.05 (.38)	.14 (.34)	-.21 [-.29, -.13]	27.63***	.35	1.53	.03	4.75*	.08	.08	.00

Note: [1]log10 scales are applied to all HRV measures; GLM df (3,52); *p<.05, **p<.01, ***p<.001; Adjusted difference [95% CI] at Group (baseline-task); There were no interactions between task*diagnostic group or task*stimulant medication use*diagnosic group; [2]Untransformed HR in beats per minute (bpm).

Table 4. GLM ANCOVA of performance measures of an auditory oddball task by diagnostic group and medication use, with age as covariate[1]

TASK	ASD+	ADHD	Adjusted	Stimulant-free	Stimulant-med	Adjusted	AGE		GROUP		MED		GROUP* MED	
	(n=20)	(n=36)	difference [95%	(n=25)	(n=31)	difference [95%								
	Mean (SD)	Mean (SD)	CI] at GROUP	Mean (SD)	Mean (SD)	CI] at STIM	F	η_p^2	F	η_p^2	F	η_p^2	F	η_p^2
Reaction Time	.13 (.02)	.13 (.02)	-.00[-.01, .01]	.14 (.02)	.13 (.02)	.01 [.00, .02]	2.19	.04	.21	.00	4.26*	.08	.07	.00
Reaction Time SD	.03 (.01)	.03 (.01)	.00 [-.00, .01]	.04 (.01)	.03 (.01)	.01 [.00, .01]	.02	.00	1.18	.02	5.57*	.10	.62	.01
Inhibition Errors	.17 (.27)	.21 (.21)	.03 [-.11, .16]	.19 (.21)	.20 (.25)	.04 [-10, .17]	2.61	.05	.15	.00	.27	.01	.52	.01
Omission Errors	.05 (.15)	.15 (.24)	.11 [-.02, .23]	.12 (.20)	.11 (.23)	-.01 [-.13, .12]	1.36	.03	3.02	.06	.02	.00	.02	.00

Note: [1] log10 scales are applied to all cardiac measures. *p<.05, **p<.01, ***p<.001; Df (4,51); Adjusted difference [95% CI] at Group (ADHD minus ASD+) at STIM (stimulant-free minus stimulant-medicated)

DISCUSSION

This study is the first to explore the psychophysiological overlap and differences in a clinical sample of adolescents diagnosed with ASD+ versus ADHD. In addition, the impact of stimulant medication use was investigated. Cardiac activity was measured during a baseline condition with eyes closed and while performing an attention task. Overall, no differences in cardiac activity or task performance were found between the ASD+ and the ADHD group. Adolescents who used stimulant medication showed increased LF/HF ratio during baseline with eyes closed, decreased LF/HF ratio adaptation from baseline to task performance and faster reaction times during task performance compared to stimulant-free adolescents.

Cardiac activity and task-related cardiac adaptation were similar for the adolescents with ASD+ and the adolescents with ADHD. Because of the supposed increased sympathetic activation associated with ASD (Bal et al., 2010; Daluwatte et al., 2012; Van Hecke et al., 2009), the expectation was that the ASD+ group would show signs of more sympathetic and less parasympathetic activation than ADHD adolescents. However, no such trend was observed in the present study. In addition, no interaction was found between medication use and diagnostic group; differences in cardiac activation and task-related cardiac adaptation between stimulant-medicated and stimulant-free adolescents, were the same within the ASD+ group and the ADHD group. This may imply that there are psychophysiological constructs related to the ADHD symptomatology, responsible for the overlap in cardiac activity between the ASD+ group and the ADHD group. However, interpreting the results it should be taken into account that sympathetic activation levels by HRV are difficult to reliably estimate (Reyes del Paso et al., 2013). The expectation was that the ASD+ group would show more sympathetic activation. Consequently, as sympathetic activation is not reflected by HRV, this also contributes to the lack of differentiation between the diagnostic groups in HRV. Furthermore, primary diagnostic groups were based on clinical diagnoses of the adolescents. Nevertheless, some adolescents with ADHD without an ASD diagnosis may experience ASD symptoms. These ASD symptoms might effect physiological measurements and thereby diminishing differences between the diagnostic groups. However, post hoc analyses with redistributed diagnostic groups based on the AQ-adolescent critical minimum score did not reveal significant differences in cardiac activity either.

The expectation that stimulant-medicated adolescents would have a higher heart rate than stimulant-free adolescents was not confirmed. Even though HR was 70 bpm for the stimulant-free adolescents and 78 bpm for the stimulant-medicated adolescents during rest condition, this difference in HR failed to reach significance after correcting for age. This in contrast to the majority of studies that show significant increases in HR of up to 10 bpm in stimulant-medicated youngsters with ADHD (Hammerness et al., 2011). This might be due to the fact that the stimulant-medicated adolescents were somewhat younger than the stimulant-free adolescents in the present study. The average HR in rest condition in the current study was 74 bpm and thereby more comparable to a HR around the 73 bpm in stimulant-free (young) adults with ADHD (Cox et al., 2012; Lackschewitz, Huther, & Kroner-

Herwig, 2008) than to the HR of approximately 85 bpm of stimulant-free school-aged children with ADHD (Donner, Michaels, & Ambrosini, 2007; Negrao et al., 2011; Wilens, Biederman, & Lerner, 2004). In addition, HR deceleration with age has been found in TD and ASD youngsters during the first years of adolescence (Daluwatte et al., 2012). Similarly, in the current study younger adolescents also displayed higher HR than the older adolescents. All in all, being a younger adolescent and using stimulant medication are both related to higher HR. Consequently, in the current study it is hard to separate the effect of stimulant medication and age.

Results from this study show that the adolescents who use stimulant medication display higher LFHF ratios during baseline rest condition with eyes closed than the stimulant-free adolescents. In addition, all adolescents in the present study showed task-related cardiac adaptation as expected with increased heart rate (HR, HR SD) and decreased time between two successive R-peaks (RR), decreased HF power and increased LFHF ratio, while performing the attention task compared to baseline. The only interaction for task-related cardiac adaptation and stimulant medication use was a decreased LFHF ratio adaptation in stimulant-medicated adolescents compared to the stimulant-free adolescents. This is in line with the study by Negrao et al. (2011) who showed that when on stimulant medication significant cardiac adaptation was no longer apparent. Although both studies point to decreased autonomic modulation for stimulant-medicated youngsters, Negrao et al. found these results for all cardiac measures, whereas the current study only found results for LFHF ratio. Whereas decreased parasympathetic activation is generally viewed as a shift to normalization, a decrease in autonomic modulation could be less favorable. It is not clear what the implications are for everyday life when stimulant-medicated youngsters are less able to shift physiologically between rest conditions and demanding cognitive activities.

The observed age effect on cardiac activity is comparable with the few available studies among healthy adolescents, in which older adolescents showed less HRV during resting baseline compared to younger adolescents (Faulkner, Hathaway, & Tolley, 2003; Tanaka et al., 2000). However, healthy adolescents show a decline in LF power, HF power *and* parasympathetic modulation with aging from pre-adolescent to adolescent (Faulkner et al., 2003; Tanaka et al., 2000). In contrast, our study showed increased LFHF ratio or autonomic modulation for older adolescents than for younger adolescents, due to decreased HF power. On the assumption that ADHD means higher levels of parasympathetic activation, this faster decline in HF power might be interpreted as normalization.

In the current study, attention task performance was alike for the adolescents with ASD+ and ADHD. However, task performance did differ depending on stimulant medication use. Stimulant-medicated adolescents responded faster and with less variability than the stimulant-free adolescents, regardless of diagnostic group. This is in line with research showing that stimulant medication primarily decreases reaction time variability in children diagnosed with ADHD (Epstein et al., 2011; Groen et al., 2008). However, previous research showed less variability in reaction time for children with ASD only versus stimulant-free children with ADHD (Groen et al., 2008). In line with a study by Althaus et al. (1999), results of the present study showed that adolescents diagnosed with ASD+ and ADHD displayed

similar reaction times. This might indicate that reaction time variability in both groups is related to the same (ADHD) symptomatology. Accuracy on the attention task did not differ between the diagnostic groups or between stimulant-medicated and stimulant-free adolescents. The amount of errors during the task for all participants was so low, that there was most likely a ceiling effect.

The current results suggest that ASD+ and ADHD adolescents may have more in common than one would expect based on previous research. Cardiac adaptation from baseline to attention task, effects of medication and effects of age were mostly as expected. Therefore, the cardiac measurement seems to be adequate to show variances in cardiac activity. Consequently, the absence of differentiation between ASD+ and ADHD is not likely to be explained by the quality of the measurement. Although results from the present study show psychophysiological overlap between ASD+ and ADHD, additional research is necessary. First, replication with a design with further controlled groups and larger sample size is warranted. The current study investigated a clinical sample of adolescents with severe ADHD symptoms. Moreover, diagnostic groups were based on clinical appointed DSM-IV diagnoses which increase the ecological validity of the study. However, further standardized information about the diagnostic process with respect to ASD is lacking. Including the Autism Diagnostic Observation Schedule (ADOS) (Lord et al., 1989) or Autism Diagnostic Interview (ADI) (Lord, Rutter, & Le Couteur, 1994) in future research will improve comparison and replication with other studies. In addition, an important limitation of the study is the absence of a group with TD adolescents. Due to the lack of this TD control group, and the absence of normal values in short time measures of cardiac activity, it is not clear if the cardiac activation of the adolescents in current study is pathological or within normal limits. Future research comparing TD adolescents and adolescents with ADHD, ASD+, and ASD-only could offer more information about which physiological patterns are specific for ASD, ADHD or typical development during adolescence. A third limitation concerns the use of stimulant medication. If applicable, adolescents continued stimulant medication as described by their physician at study entry. Therefore, initial differences between stimulant-medicated and stimulant-free adolescents could not be controlled for. Ideally, psychophysiological measures should be taken at two moments in time: the first before starting stimulant medication or after a washout of stimulant medication and second after a controlled stimulant medication titration trial. At least, an improvement should entail a more equal division of age between the stimulant-medicated adolescents and the stimulant-free adolescents. In the current study, adolescents who used stimulant medication were younger than the adolescents who were not on stimulant medication. Consequently, it is difficult to distinguish between the effect of stimulant medication and age. A fourth limitation is that baseline parameters were measured for a relatively short period. Although the Task Force (1996) states that approximately two minutes of recording are sufficient to measure LF power, the same report advises a minimum of ten times the wavelength. A baseline of at least five minutes might therefore be preferable for more reliable baseline measures of LF power and LFHF ratio. Finally, future studies should include additional physiological measures, such as EEG, to see whether it can be related to more specific ADHD symptomatology, like attention processing.

In conclusion, the present study showed a psychophysiological overlap in cardiac reactivity and in cognitive performance measures between adolescents with ASD+ and ADHD. Effects of stimulant medication did not appear to differ between the groups. As such, our study suggests that ADHD with or without ASD could be approached with similar treatment strategies. The current results support the idea of, for instance, Gadow et al. (2006), Goldstein and Schwebach (2004) and the DSM-V task force (American Psychiatric Association, 2012) for a comorbid diagnosis of ADHD in addition to ASD. A comorbid diagnosis of ADHD might thereby help prevent that ASD+ youngsters are excluded from potentially beneficial ADHD treatment.

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CHAPTER 3

EEG Theta power discriminates adolescents with ADHD from adolescents with ASD+ADHD

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ABSTRACT

Attention problems are common in youngsters with attention deficit hyperactivity disorder (ADHD) as well as in adolescents with combined autism spectrum disorder (ASD) and ADHD. However, it is unknown whether there is psychophysiological overlap and/or a difference in electroencephalogram (EEG) power spectra between ADHD and comorbid ASD and ADHD (ASD+ADHD), on and off stimulant medication. In order to explore potential differences and overlap, measures of theta and beta power in adolescents diagnosed with ADHD (n=33) versus adolescents with combined ASD+ADHD (n=20), categorized by stimulant medication use (57% of the total sample), were compared. EEG measures were acquired in three conditions: (1) resting state, eyes closed, (2) resting state, eyes open and (3) during an oddball task. In addition performance on the d2 attention test was analyzed. Adolescents with ADHD displayed more absolute theta activity than adolescents with ASD+ADHD during the eyes open and task conditions, independent of stimulant medication use. In addition, only the adolescents with ADHD showed an association between diminished attention test performance and increased theta in the eyes open condition. Results of the current study suggest that although there is behavioral overlap between ADHD characteristics in adolescents with ADHD and adolescents with combined ASD+ADHD, the underlying psychophysiological mechanisms may be different. Adolescents with ASD+ADHD exhibited fewer of the EEG physiological signs usually associated with ADHD, although there was an overlap in attentional problems between the groups. This may indicate that treatments developed for ADHD work differently in some adolescents with ASD+ADHD and adolescents with ADHD only.

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) co-occurs with autistic spectrum disorders (ASDs) in around 28 percent of youngsters with ASD (Simonoff et al., 2008). Stimulant medication, part of the gold standard treatment for ADHD, is also prescribed in cases of comorbid ASD and ADHD (ASD+ADHD). However, the reported stimulant medication response rate of 49% in ASD+ADHD (Research Units on Pediatric Psychopharmacology (RUPP) Autism Network, 2005) is lower than the 77% response rate in ADHD (Greenhill et al., 2001). This suggests that although there is behavioral overlap between ADHD with and without ASD, the psychophysiological mechanisms underlying attentional problems may be different in these groups.

Electro-encephalogram (EEG) power spectra have often been used to assess psychophysiological functioning in ADHD. The most robust finding in ADHD is increased theta power (Cortese, 2012; Loo & Makeig, 2012; Snyder & Hall, 2006) mainly in frontocentral areas (Loo & Makeig, 2012) and, to a lesser extent, decreased beta activity (Cortese, 2012; Snyder & Hall, 2006). The theta (4-7Hz) and beta (13-30Hz) bands of the power spectrum have been related to measures of vigilance and attention respectively, at the behavioral level (Banaschewski & Brandeis, 2007), and during childhood show maturational changes: decreasing slow wave activity (including theta) and increasing fast wave activity (including beta) (John et al., 1980). Specifically, theta power seems to be negatively associated with vigilance or alertness, with high theta corresponding to an underaroused (Banaschewski & Brandeis, 2007; Loo & Barkley, 2005; Loo & Makeig, 2012) and unfocused state (Loo & Barkley, 2005). In contrast, beta power seems to be positively associated with attention (Banaschewski & Brandeis, 2007; Loo & Barkley, 2005; Loo & Makeig, 2012), with decreased beta also associated with an unfocused state (Banaschewski & Brandeis, 2007). Lubar (1991) therefore proposed theta/beta ratio as an indicator of ADHD, and indeed, increased theta/beta ratio is found in some youngsters with ADHD (Arns, Conners, & Kraemer, 2013; Barry, Clarke, & Johnstone, 2003; Snyder & Hall, 2006). As a whole, the theta and beta data provide support for the hypothesized maturational lag (Clarke, Barry, McCarthy, & Selikowitz, 1998) and in the seventies generated underarousal theories of ADHD (Satterfield, Cantwell, & Satterfield, 1974).

The abnormal pattern of theta and beta activity in youngsters with ADHD can be partly normalized by stimulant medication use (Clarke, Barry, Bond, McCarthy, & Selikowitz, 2002; Clarke, Barry, McCarthy, Selikowitz, Brown, et al., 2003; Hermens, Williams, et al., 2005; Loo & Barkley, 2005), which typically decreases theta activity and increases beta activity. A subpopulation of youngsters with ADHD show excessive frontal beta instead of decreased beta (Clarke, Barry, McCarthy, & Selikowitz, 2001b). These youngsters respond differently to stimulant medication, showing a reduction in beta and total power (Clarke, Barry, McCarthy, Selikowitz, Clarke, et al., 2003). Overall, it seems that stimulant medication in youngsters with ADHD results in power spectra that are more similar to those of typically developing (TD) youngsters.

Youngsters with ASD show increased relative theta compared to TD youngsters (Coben, Clarke, Hudspeth, & Barry, 2008; Murias, Webb, Greenson, & Dawson, 2007), similar to youngsters with ADHD

(Chabot & Serfontein, 1996; Clarke et al., 2002; Clarke et al., 1998; Clarke, Barry, McCarthy, & Selikowitz, 2001a). In addition to increased relative theta, youngsters with ASD also show differences in absolute and relative beta; however, studies show mixed results. Adults with ASD show increased occipital relative beta (Murias et al., 2007) and young children with ASD have been shown to have increased absolute beta (Orekhova et al., 2007) relative to TD participants, but there is also a finding of decreased absolute beta, particularly in the right hemisphere, in children with ASD (Coben et al., 2008). EEG power spectra in children with a primary diagnosis of ADHD and ASD have been little studied. The clearest result of the only study that compared children with a primary diagnosis of ADHD with and without autistic characteristics (Clarke, Barry, Irving, McCarthy, & Selikowitz, 2011) was an increase in relative beta in children with ADHD with autistic characteristics compared to those with only ADHD. Although theta power did not differentiate the groups, this study also found a greater increase in theta from frontal to central regions in children with autistic characteristics (Clarke et al., 2011); it must be noted that in this study no formal DSM-IV (American Psychiatric Association, 2000) diagnosis of ASD was required. Taken together, these findings may point to a psychophysiological dissociation between ADHD with and without ASD, despite the behavioral overlap between the conditions.

Previous research on the psychophysiological effects of stimulant medication has focused mainly on adolescents with ADHD (Clarke et al., 2002; Clarke, Barry, McCarthy, Selikowitz, Brown, et al., 2003; Hermens, Williams, et al., 2005; Loo & Barkley, 2005). The relationship between attentional problems and EEG power spectra in ADHD and ASD+ADHD, both on and off medication remains unknown. A better understanding of potential underlying differences between the conditions could explain why adolescents with ASD+ADHD (RUPP, 2005) have a less favorable response to stimulant medication than adolescents with ADHD (Greenhill et al., 2001). If the underlying mechanisms of the conditions are similar, attentional problems in ASD+ADHD might be treated similarly to those in ADHD, for example with stimulant medication; however, differences in EEG power spectra between ADHD and ASD+ADHD would suggest that treatment options for the attentional problems should be specific to each subgroup. This study aimed to explore psychophysiological differences between these groups in terms of EEG power spectra, comparing stimulant-medicated and stimulant-free adolescents with a primary diagnosis ADHD with adolescents with a combined diagnosis of ASD and ADHD. We predicted an overlap in theta power and a specific increase in absolute and relative beta levels in adolescents with ASD+ADHD compared to adolescents with ADHD only. Furthermore, in line with previous studies (Clarke et al., 2002; Clarke, Barry, McCarthy, Selikowitz, Brown, et al., 2003; Hermens, Williams, et al., 2005; Loo & Barkley, 2005), we predicted that stimulant-medicated adolescents would show less absolute and relative theta power, and a corresponding decrease in theta/beta ratio compared with stimulant-free adolescents.

METHOD

Participants

This study used a sample of 53 adolescents recruited for an intervention study for adolescents with clinical ADHD symptoms. Prior to the start of the study, approval was obtained from the Medical Ethics Committee for Mental Health Institutions in the Netherlands (Ref. no: NL 24776.097.08 CCMO). The study took place in three centers of child and adolescent psychiatry (GGzE, GGz Breburg, Reinier van Arkel group) in the southern part of the Netherlands. Written informed consent was obtained from all participants. For participants aged less than 18 years, parents also provided written informed consent. The sample was the same as in Bink et al. (2013), with the exclusion of five adolescents because of poor quality of the EEG data and the addition of two patients: one who enrolled later in the study and one who had been excluded from the earlier study because of missing oddball task-performance data. This patient was included as the EEG data could be used.

Two diagnostic groups of male adolescents aged between 12 and 22 years old were included in the study. The first group consisted of 33 adolescents with a clinical DSM-IV(American Psychiatric Association, 2000) primary diagnosis of ADHD, including: combined subtype (n=16), inattentive subtype (n=16), and hyperactive/ impulsive subtype (n=1). The second group consisted of 20 adolescents with a primary diagnosis of ASD, including: Asperger's syndrome (n=6) and pervasive developmental disorder – not otherwise specified (PDD-NOS; n=14). Adolescents with ASD also had a notification of clinical ADHD with symptoms sufficient for a full ADHD diagnosis. ADHD symptoms were verified by a DSM-IV based Dutch semi-structured ADHD interview for adults (Kooij, 2002) and the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998; Sheehan et al., 1997). Exclusion criteria were IQ<80, neurological disorders, schizophrenia and other psychotic disorders, depression, attachment disorder or anxiety disorder, medication use other than stimulant medication and use of cannabis in the 24 hours prior to physiological assessment.

Stimulant medication use was monitored through an intervention questionnaire based on the Dutch national basic ADHD program for children and adolescents (Vink & Van Wamel, 2007). Adherence to prescribed medication was verified by asking the adolescents whether they had been taking their medication as prescribed before the EEG measurement. In total, 30 (57%) of the adolescents used stimulant medication. In the ADHD group, 19 (58%) used stimulant medication: 6 used immediate release methylphenidate and 13 used sustained release methylphenidate. In the ASD+ADHD group, 11 (55%) used stimulant medication: 1 used immediate release methylphenidate and 10 used sustained release methylphenidate. Two adolescents in the ASD+ADHD group used low doses (0.5mg and 1.5mg per day) of antipsychotic medication (Risperdal®) in addition to their stimulant medication. Because the doses were low, in combination with stimulant medication use, potential impact on the outcome measures was considered minimal.

Comorbid disorders were allowed: included in the ADHD group were participants with substance-related disorders (*n*=2), conduct disorders (*n*=3), and reading disorder (*n*=2). In the ASD+ADHD group participants with conduct disorder (*n*=1) and reading disorder (*n*=1) were included.

Measures

Group characteristics

The group characteristics are listed in Table 1. The measures reported are Global Assessment of Functioning (GAF) score, the DSM-IV (American Psychiatric Association, 2000) based ADHD-rating scale (Kooij et al., 2008; Kooij et al., 2005) which is an adapted form of DuPaul et al. (1998), the MINI subscales for inattention and hyperactivity/impulsivity (HI), the Autism-Spectrum Quotient (AQ)-adolescent version for individuals with normal intelligence (Baron-Cohen, Hoekstra, Knickmeyer, & Wheelwright, 2006; Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001), the Child Behavior Checklist (CBCL) and the Youth Self Report (YSR) (Achenbach, 1991), and the WISC-III or the WAIS-III full-scale total intelligence quotient (TIQ) (Wechsler, 1991, 1997). Further information about the reported group characteristics can be found elsewhere (Bink et al., 2013)

Cognitive measures

The d2 attention test (Brickenkamp, 2007) was administered and the raw scores of the total number of processed items (TN) and total correctly processed items (C) were analyzed.

Physiological measures

The EEGs were recorded between 10am and 11am. Where applicable, stimulant medication was taken with breakfast, before the measurement. No caffeine or nicotine intake was allowed during the two hours prior to physiological assessment.

The EEG recordings were performed in combination with a subset of the Brain Resource Company (BRC; Ultimo, Australia) test battery. This included a baseline condition in which participants had to sit quietly with their eyes open for two minutes and closed for two minutes. Subsequently, they performed an auditory oddball task lasting 6 minutes. EEGs were recorded using the 10-20 system using a Quick-Cap with 26 EEG electrodes and impedance <5kΩ. Horizontal electrooculograms (EOG) were recorded with two electrodes placed 1.5cm lateral to the lateral canthi of the eyes. Vertical EOGs were recorded with electrodes above and below the middle of the eye with the upper electrode placed 3mm above the eyebrow and the other electrode 1.5cm below the lower eye-lid. A Neuroscan NuAmps amplifier recorded the signals with a sampling frequency of 500Hz, 100Hz low-pass anti-aliasing filter, and 32 bit, DC high-pass filter.

EEG-recordings were analyzed with Brain Vision Analyzer v2.0 (Brain Products GmbH, Germany). Reference to linked mastoids was calculated off-line; a high-pass filter of 0.5Hz, 12dB/octave and a low-pass filter of 30Hz, 48dB/octave were applied. Ocular correction was applied as in Gratton, Coles, and Donchin (1983). Data were segmented in 2s epochs. Automatic raw data inspection was

applied with a maximum allowed voltage step between samples of 50μV/ms, maximum allowed difference of 120μV in each segment, and permitted amplitude range of -100μV-100μV. Data were marked as bad 200ms before and after a detected artifact, the lowest permitted activity in intervals was 0.5μV with an interval length of 50ms. Fast Fourier Transformation (FFT) with a 20% Hamming window was applied for tapering, and averages over the artifact-free epochs per channel were calculated. At least 30 artifact free epochs had to be available for a channel to be included. Mean included channels were for eyes closed condition: M=25.64, SD=.92; eyes open condition: M=25.89, SD=.32 and task condition: M=25.87, SD=.34, and did not differ between the diagnostic groups (eyes closed: F=.06, ηp2=.00, p>.05; eyes open: F=.42, ηp2=.01, p>.05; task: F=.09, ηp2=.00, p>.05) nor with stimulant medication use (eyes closed: F=.05, ηp2=.00, p>.05; eyes open: F=.12, ηp2=.00, p>.05; task: F=.00, ηp2=.00, p>.05). In addition, for each condition the number of epochs for the channel with the fewest epochs (minimum epochs) was considered. The mean minimum epochs were eyes closed: M=57.64, SD=8.04; eyes open: 58.81, SD=4.35 and task: M=172.66, SD=21.72, and did not differ between the diagnostic groups (eyes closed: F=.32, ηp2=.01, p>.05; eyes open: F=.03, ηp2=.00, p>.05; task: F=.13, ηp2=.00, p>.05) nor according to stimulant medication use (eyes closed: F=.05, ηp2=.00, p>.05; eyes open: F=.30, ηp2=.01, p>.05; task: F=1.76, ηp2=.03, p>.05). Mean absolute power (μV2) was exported to SPSS for the following frequency bands: delta 1.5-3.5Hz, theta 3.5-7.5Hz, alpha 7.5-12.5Hz, beta 12.5-25Hz and total power 1.5-25Hz. To increase the comparability of the results the frequency bands used were similar to those used in previous studies in ADHD by Clarke et al. (Clarke et al., 2002; Clarke et al., 2011; Clarke et al., 2001b; Clarke, Barry, McCarthy, Selikowitz, Brown, et al., 2003; Clarke, Barry, McCarthy, Selikowitz, Clarke, et al., 2003). Relative power was calculated as the absolute power per frequency band divided by the total power (1.5-25 Hz). A log10 transformation was applied to all absolute and relative measures to give a Gaussian distribution.

Initial regions of interest (ROIs) were based on a principal components analysis (PCA) of the frequency bands for the electrodes with covariance matrix, varimax rotation and Kaiser normalization. Missing values were replaced by mean imputation. Two regions were defined for the different conditions and frequency bands: frontocentral (Fp1, Fp2, F7, F3, Fz, F4, F8, FC3, FCz, FC4, C3, Cz, C4, CP3, CPz, CP4, T3, T4) and parietal-occipital (P3, Pz, P4, O1, Oz, O2, T5, T6). To improve comparability with areas defined in other reports three ROIs were derived: anterior (Fp1, Fp2, F7, F3, Fz, F4, F8, FC3, FCz, FC4), central (C3, Cz, C4, Cp3, CPz, Cp4, T3, T4) and posterior (P3, Pz, P4, O1, Oz, O2, T5, T6). ROI values were therefore calculated for the different frequency bands across the three conditions as the mean of the respective electrodes.

Data analyses

All analyses were performed using SPSS version 19.0. Differences in group characteristics were analyzed with a one-way ANOVA or a chi-square test ($\chi 2$) with Fisher exact correction. Generalized Linear Model (GLM) univariate ANCOVAs were conducted for the measures of the d2 test of attention, with age as

covariate and diagnostic group (ADHD or ASD+ADHD) and stimulant medication use (stimulant-medicated and stimulant-free) as between-subjects factors. GLM repeated-measures (RM) ANCOVAs were conducted separately for the absolute and relative power measures, with age as covariate, ROI as within-subject factor, and diagnostic group and stimulant medication use as between-subjects factors. The full factorial models were tested. All ROI effects were evaluated using multivariate test criteria, a method known to be robust against violations of sphericity (Vasey & Thayer, 1987). In addition, where applicable, the least significant difference (LSD) adjusted difference (AD) and 95% confidence interval (95% CI) have been reported. Significant three-way between-groups interactions were investigated with separate post-hoc GLM RM ANCOVA for each stimulant medication condition (on and off stimulant medication), with age as covariate, ROI as within-subject factor and diagnostic group as between-subjects factor. Effect sizes are expressed as proportion of explained variance in partial $\eta 2$ (η_p^2). In this study, absolute theta, absolute beta, total power, relative theta, relative beta and the theta/beta ratio were considered. (For an overview of the total power spectrum including delta and alpha see eSupplement 1).

Post-hoc stepwise linear regressions were performed separately for diagnostic group (ADHD and ASD+ADHD) with the measures of the d2 attention test (TN and C) as dependent variables. Four sets of independent variables were analyzed in each behavioral condition (eyes closed, eyes open and task) for all ROIs: (1) absolute theta, (2) relative theta, (3) absolute beta, and (4) relative beta. Because of multicollinearity between the independent variables, only the variable with the strongest association to the d2 test attention measures was considered. Values of $p<.05$ were considered statistically significant. The current study was exploratory so no alpha correction for multiple testing was applied.

RESULTS

Group characteristics

Group characteristics are summarized in Table 1. The two diagnostic groups (ADHD and ASD+ADHD) did not differ in age (see Table 1). In total 30 (57%) adolescents used stimulant medication. Stimulant medication use was equally distributed over the diagnostic groups, with 19 (58%) adolescents with ADHD and 11 (55%) with combined ASD+ADHD using stimulant medication, $\chi 2(1, 51)=.00$, $p>.05$. In addition, the mean prescribed dose in mg for the stimulant-medicated adolescents was similar in the ADHD group ($n=19$, M=34.74, SD=13.02), and the ASD+ADHD group ($n=11$, M=35.27, SD=17.35; $F(1, 28)=.01$, $p>.05$, $\eta_p^2=.00$). However, the average age of the stimulant-free adolescents (ADHD: M=16.21, SD=3.87; ASD+ADHD: M=16.78, SD=2.54) was somewhat older than that of the stimulant-medicated adolescents (ADHD: M=14.64, SD=2.38; ASD+ADHD: M=14.63, SD=2.19). This age difference was similar in the ADHD group and the ASD+ADHD group, ($F(3,49)=.12$, $p>.05$, $\eta_p^2 =.00$. Stimulant-free and stimulant-medicated adolescents did not differ significantly on other group characteristics.

The AQ adolescent confirmed that the ASD+ADHD group exhibited more autism symptoms than the ADHD group. For the ASD+ADHD group, parents reported more total behavioral problems on the CBCL. The two diagnostic groups did not differ on other group characteristics.

Table 1. Group characteristics[a]

	TOTAL	ASD+ADHD	ADHD	F	η_p^2	Stimulant-medicated	Stimulant-free	F	η_p^2
	n=53	*n*=20	*n*=33			*n*=30	*n*=23		
	Mean (SD)	Mean (SD)	Mean (SD)			Mean (SD)	Mean (SD)		
Age in Years	15.42(2.88)	15.60(2.62)	15.30(3.07)	.13	.00	14.63(2.22)	16.43(3.36)	5.52*	.10
GAF-score	55.11(6.45)	54.50(6.10)	55.48(6.73)	.29	.01	55.00(6.65)	55.26(6.33)	.02	.00
AQ-adolescent version[b]	25.58(8.02)	32.45(5.36)	21.41(6.33)	42.35***	.45	24.63(8.10)	26.80(7.93)	.95	.02
ADHD-rating scale[c]									
Inattention	4.75(2.24)	4.90(2.25)	4.67(2.26)	.13	.00	4.47(2.22)	5.13(2.24)	1.15	.02
Hyperactivity/Impulsivity (H/I)	3.45(1.89)	3.70(2.06)	3.30(1.79)	.55	.01	3.73(1.96)	3.09(1.76)	1.54	.03
Childhood Inattention	6.04(2.67)	5.65(2.83)	6.27(2.58)	.67	.00	6.07(2.68)	6.00(2.71)	.01	.00
Childhood H/I	4.94(2.78)	4.20(2.75)	5.39(2.75)	2.35	.04	5.10(2.80)	4.74(2.82)	.22	.00
MINI ADHD Inattention	5.38(2.48)	5.00(2.53)	5.61(2.46)	.74	.01	5.27(2.50)	5.52(2.50)	.14	.00
MINI ADHD H/I	3.72(2.26)	3.60(2.39)	3.79(2.22)	.08	.00	3.80(2.14)	3.61(2.46)	.09	.00
CBCL Total Problems	62.57(28.89)	72.95(28.27)	56.27(27.81)	4.42*	.08	59.63(26.08)	66.39(32.39)	.71	.01
Internalizing Problems	14.47(9.54)	17.55(10.37)	12.61(8.62)	3.51	.06	13.00(7.71)	16.39(11.39)	1.67	.03
Externalizing Problems	18.79(11.53)	21.80(11.06)	16.97(11.59)	2.24	.04	17.80(10.68)	20.09(12.68)	.51	.01
Attention Problems	11.83(3.50)	12.80(3.62)	11.24(3.34)	2.55	.05	11.87(3.30)	11.78(3.81)	.01	.00
YSR Total Problems	47.42(20.58)	54.30(21.43)	43.24(19.18)	3.79	.07	46.03(17.47)	49.21(24.35)	.31	.01
Internalizing Problems	9.17(5.79)	10.90(6.09)	8.12(5.43)	2.97	.06	8.70(5.33)	9.78(6.42)	.45	.01
Externalizing Problems	15.51(9.66)	17.85(9.89)	14.09(9.38)	1.92	.04	14.97(9.04)	16.22(10.57)	.22	.00
Attention Problems	9.26(3.14)	8.85(3.59)	9.52(2.87)	.55	.01	9.10(2.89)	9.48(3.50)	.19	.00
TIQ	101.83(10.74)	104.90(11.60)	99.97(9.90)	2.71	.05	102.53(11.75)	100.91(9.44)	.29	.01

Note: *p<.05, **p<.01, ***p<.001; [a] Data are means (SD); df (1,51); [b] Autism Spectrum Quotient (AQ)- adolescent version is a parent report; [c] The ADHD-rating subscales are retrospective self-reported current and childhood symptoms; H/I = Hyperactivity/Impulsivity

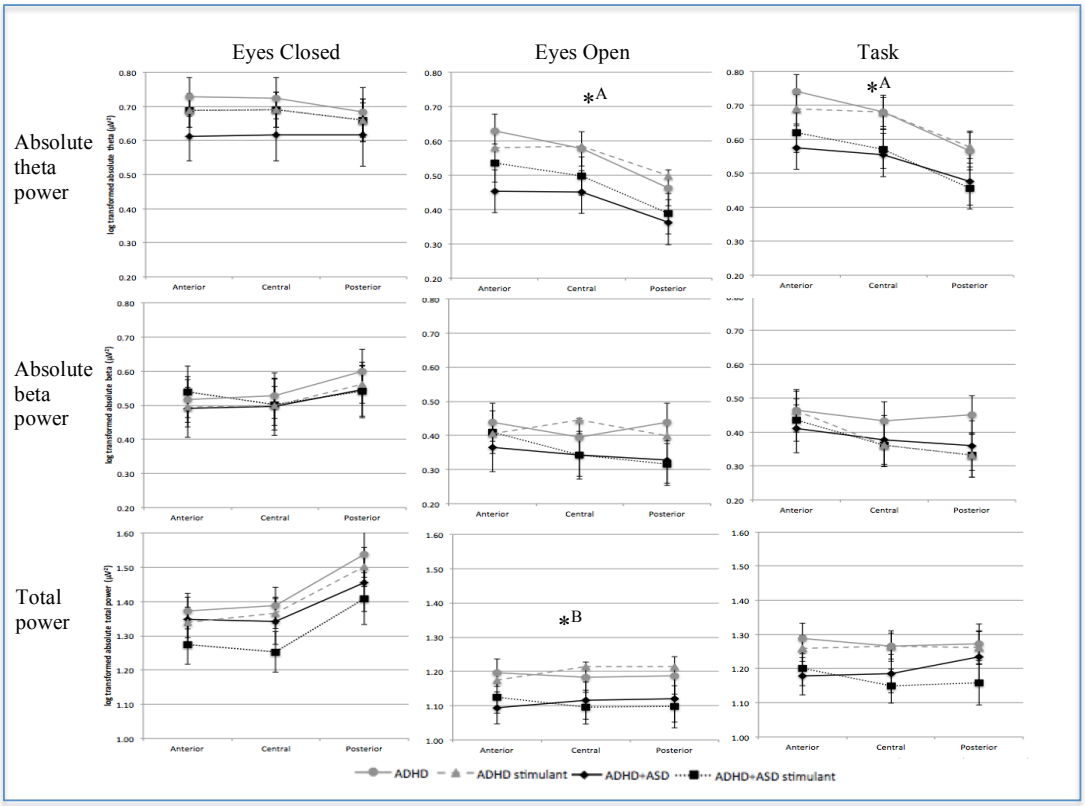
Cognitive performance

D2 attention test performance (TN and C) was similar for the two diagnostic groups, see Table 2. In addition, stimulant-free and stimulant-medicated adolescents did not differ in terms of d2 attention test performance. Older adolescents performed better than younger adolescents in terms of both TN and C.

EEG

EEG outcomes are summarized in Table 3 and absolute measures are shown in Figure 1.

Figure 1. *Absolute power as a function of region for the ADHD and ASD+ADHD groups, on and off stimulant medication*



Note: Estimated marginal means are shown for log transformed absolute power (μV2) with standard error bars for each ROI and the evaluated covariate age 15.42 years for each condition (eyes closed, eyes open and task), for stimulant-free and stimulant-medicated adolescents with ADHD and for stimulant-free and stimulant-medicated adolescents with ASD+ADHD; *[a] Absolute theta was higher during the eyes open and task conditions for adolescents with ADHD than adolescents with ASD+ADHD, irrespective of stimulant medication use; *[b] Total power increased from the anterior ROI to the central ROI in stimulant-medicated adolescents with ADHD during the eyes open condition.

Diagnostic group and stimulant medication use

Absolute theta power differed between the adolescents with ADHD and the adolescents with ASD+ADHD during the eyes open and task conditions. During the eyes open condition, adolescents with ADHD displayed more absolute theta than adolescents with ASD+ADHD, $AD_{ADHD\text{-}ASD+ADHD}$=.11, 95%CI:.004-.21, p<.05. During the task condition adolescents with ADHD also showed more absolute theta than adolescents with ASD+ADHD, $AD_{ADHD\text{-}ASD+ADHD}$=.11, 95%CI:.01-.22, p<.05. There was no

diagnostic group difference in absolute theta during the eyes closed condition. Differences in absolute theta are shown in Figure 1. There were no main effects of stimulant medication use on absolute theta and no interaction involving stimulant medication use. Absolute beta power and theta/beta ratio revealed no main effects of diagnostic group or stimulant medication use.

There was an interaction between ROI, diagnostic group, and medication use on total power in the eyes open condition (see Table 3 and Figure 1). Post-hoc analyses showed an interaction between ROI and diagnostic group for stimulant-medicated adolescents, $F(2,26)=4.40$, $p<.05$, $\eta p2=.25$, whereas in stimulant-free adolescents this interaction was not significant, $F(2,19)=.72$, $p=.50$, $\eta p2=.07$. Figure 1 shows that in the eyes open condition the interaction is more pronounced in the anterior region than the central region. Post-hoc analysis of the central and anterior ROIs confirmed this, showing an interaction between ROI and diagnostic group in stimulant-medicated adolescents, $F(1,27)=8.81$, $p<.01$, $\eta p2=.25$, but not in stimulant-free adolescents, $F(1,20)=1.51$, $p=.23$, $\eta p2=.07$. Stimulant-medicated adolescents with ADHD showed more total power in the central region than the anterior region, ADcentral-anterior=.04, 95%CI:.01-.08, $p<.01$. For adolescents with combined ASD+ADHD there was no significant difference between central and anterior regions, ADcentral-anterior=-.03, 95%CI:-.06-.01, $p>.05$. In summary, stimulant-medicated adolescents with ADHD showed an increase in total power from the anterior region to central region. Relative theta and relative beta did not differ between stimulant-free and stimulant-medicated adolescents, nor was there an overall interaction between the two diagnostic groups on and off medication.

Age effects

Age by topography interactions are summarized in Table 3. For detailed information about the effects of age see eSupplement 1. Note: age was taken into consideration because the mean age of stimulant-medicated adolescents was younger than that of stimulant-free adolescents.

There was an overall decrease in absolute power with age. Specifically, the reduction of absolute theta power in older adolescents during the eyes closed condition was greatest in the posterior region and smaller at more anterior scalp locations. During the eyes open and the task conditions a general decrease in absolute theta with age was seen. Absolute beta power decreased with age during the eyes open and the task conditions. There was a corresponding general decrease in theta/beta ratio with age during the eyes closed and task conditions. Reductions in theta/beta ratio in older adolescents during the eyes open condition were greatest in the posterior regions and smaller at more anterior scalp locations. In all three conditions there was a general decrease in total power with age. Relative theta did not change with age. In contrast, relative beta increased with age during the eyes closed and task conditions. During the eyes open condition the increase in relative beta was greatest in the posterior region and smaller at more anterior scalp locations. In summary, absolute power decreased with age for most frequency bands and only relative beta showed an increase in all three conditions. In general age effects were most pronounced in the posterior region.

Table 2. GLM ANOVA of the d2 attention test with age as covariate [a]

	TOTAL	ASD+ADHD	ADHD	Diagnostic group		Stimulant-medicated	Stimulant-free	Stimulant medication		Age		
	Mean (SD)	Mean (SD)	Mean (SD)	F	η_p^2	Mean (SD)	Mean (SD)	F	η_p^2	F	η_p^2	B_{AGE}
D2 attention test	*n*=53	*n*=20	*n*=33			*n*=30	*n*=23					
Total Processed Items (TN)	421.60 (67.96)	422.35 (70.27)	421.15 (67.61)	.06	.00	419.33 (62.24)	424.57 (76.11)	1.89	.04	25.65***	.35	14.64***
Total Correct Items (C)	164.75 (26.17)	166.15 (32.73)	163.91 (21.78)	.00	.00	164.60 (25.01)	164.96 (28.17)	2.11	.04	20.41***	.29	5.22***

Note: *p<.05, **p<.01, ***p<.001; [a]Data are means (SD); df (1,48)

Table 4. Dependence of the d2 attention test on theta and beta power for ADHD and ASD+ADHD groups

			ADHD (*n*=33)				**ASD+ADHD** (*n*=20)			
Frequency band	D2	Condition	ROI	β	R^2	F (1,31)	ROI	β	R^2	F (1,18)
Absolute theta	**TN**[a]	Eyes closed	Central	-.580	.337	15.74***	Posterior	-.548	.300	7.71***
	C[b]	Eyes closed	Central	-.409	.167	6.22*	-	-	-	-
	TN[a]	Eyes open	Posterior	-.605	.366	17.91***	-	-	-	-
	C[b]	Eyes open	Posterior	-.462	.213	8.41**	-	-	-	-
	TN[a]	Task	Posterior	-.581	.338	15.82***	Posterior	-.469	.220	5.08*
	C[b]	Task	Posterior	-.430	.185	7.04*	-	-	-	-
Relative theta	**TN**[a]	Eyes closed	Central	-.353	.125	4.42*	-	-	-	-
Absolute beta	**TN**[a]	Eyes open	Central	-.355	.126	4.46*	-	-	-	-
	TN[a]	Task	Central	-.464	.215	8.51**	-	-	-	-
Relative beta	**TN**[a]	Eyes open	Posterior	.435	.189	7.22*	Posterior	.465	.216	4.96*
	TN[a]	Task	Posterior	.359	.129	4.60*	Posterior	.493	.243	5.77*

Note: Separate stepwise regressions were performed for the ADHD, df(1,31), and the ASD+ADHD group df(1,18).
TN and C were the dependent variables. Independent variables were: (1) absolute theta, (2) relative theta, (3) absolute beta, and (4) relative beta.
Only significant models are reported, β= standardized regression coefficients, * p<.05, ** p<.01, *** p<.001; [a]TN= total processed items,
[b]C= total correct items.

Table 3. EEG results for each frequency band by region, diagnostic group, stimulant medication use and age

Condition	Frequency band		ROI [a]		ADHD or ASD+ADHD		ROI, ADHD or ASD+ADHD and Stimulant Medication		Age		ROI and Age	
			F(2,47)	η_p^2	F(1,48)	η_p^2	F(2,47)	η_p^2	F(1,48)	η_p^2	F(2,47)	η_p^2
Eyes Closed	Absolute	Theta	2.79†	.11	2.38	.05	.57	.02	25.72***	.35	3.82*	.14
	Absolute	Beta	4.44*	.16	.04	.00	.33	.01	2.27	.05	2.34	.09
	Total	Power	3.83*	.14	1.48	.00	.60	.02	20.21***	.30	1.31	.05
	Relative	Theta	1.15	.05	.54	.00	1.65	.07	2.98	.06	.78	.03
	Relative	Beta	1.28	.05	.91	.02	.46	.02	6.90*	.13	.98	.04
	Ratio	Theta/beta	1.67	.07	.28	.03	.33	.01	9.68***	.17	1.34	.05
Eyes Open	Absolute	Theta	1.78	.07	4.32*	.08	2.98	.11	32.54***	.40	2.98	.11
	Absolute	Beta	1.05	.04	1.59	.03	2.60	.10	5.09*	.10	.65	.03
	Total	Power	2.41	.09	3.46†	.07	3.90*	.14	28.24***	.37	2.33	.09
	Relative	Theta	1.48	.06	.50	.01	.62	.03	2.55	.05	.32	.01
	Relative	Beta	5.47**	.19	.17	.00	.71	.03	8.43**	.15	4.25*	.15
	Ratio	Theta/beta	2.71†	.10	.40	.01	1.44	.06	8.19**	.15	3.59*	.13
Task	Absolute	Theta	.52	.02	4.52*	.09	1.96	.08	31.91***	.40	2.43	.09
	Absolute	Beta	.12	.01	1.54	.03	1.18	.05	5.08*	.10	.04	.00
	Total	Power	1.96	.08	2.95†	.06	3.04	.11	26.58***	.36	2.30	.09
	Relative	Theta	2.54	.10	1.10	.02	.23	.01	3.00	.06	.04	.00
	Relative	Beta	2.51	.10	.10	.00	.67	.03	8.77**	.15	1.67	.07
	Ratio	Theta/beta	.55	.02	.53	.01	1.05	.04	8.91**	.16	1.15	.05

Note: *=p<.05, **=p<.01, ***=p<.001; [a]The regions of interest (ROIs) Anterior, Central and Posterior were included. Variables and interactions were included in the table only if there was a significant main effect of the variable or an interaction for at least one of the frequency bands. Stimulant medication showed no between-groups effect and was therefore not included

Region

During the eyes closed condition absolute beta and total power differed across ROIs (see also Figure 1). Absolute beta was greatest in the posterior region, $AD_{posterior\text{-}anterior}$=.05, 95%CI:.02-.09, p<.01; $AD_{posterior\text{-}central}$=.06, 95%CI: .03-.08, p<.001. Similarly, total power was greatest in the posterior region, $AD_{posterior\text{-}anterior}$ =.14, 95%CI:.10-.19, p<.01; $AD_{posterior\text{-}central}$= .06, 95%CI:.03-.08, p<.001. Relative beta during the eyes open condition showed activity mainly at anterior sites, $AD_{anterior\text{-}central}$=.03, 95%CI:.003-.05, p<.05; $AD_{anterior\text{-}posterior}$=.04, 95%CI:.01-.08, p<.05.

Post-hoc d2 attention test performance, theta and beta power

In Table 4, the associations between d2 attention test performance and absolute and relative power are summarized separately for the two diagnostic groups. Low absolute theta the during eyes closed condition was associated with a higher TN than high absolute theta; in the ADHD group this applied to central theta and in the ASD+ADHD group it applied to posterior theta. During the eyes open condition, low posterior theta was associated with a higher TN in the ADHD group, but not in the ASD+ADHD group. During the task condition low posterior theta was associated with a higher TN than high posterior theta in both diagnostic groups. The ADHD group also showed an association between low theta and C in the central regions during the eyes closed condition and in the posterior region during the eyes open and task conditions. C was not related to theta in the ASD+ADHD group. Low relative theta in the central region during the eyes closed condition was associated with high TN in the ADHD group, but not in the ASD+ADHD group. In the other conditions there were no associations between relative theta and d2 attention test performance.

Low absolute central beta during the eyes open and task conditions was associated with high TN in the ADHD group, but not in the ASD+ADHD group. High posterior relative beta during the eyes open and task conditions was associated with high TN in both diagnostic groups.

Overall, absolute theta was associated with attention test performance, in all three conditions in the ADHD group. There was an association between relative theta and TN in the eyes closed condition, but only in the ADHD group. In the ASD+ADHD group there was an association between posterior absolute theta and TN during the eyes closed and task conditions. High relative beta seems to be associated with better performance in both diagnostic groups. In general, the associations between attentional performance and relative beta were most pronounced in the posterior region.

DISCUSSION

The current study explored differences between adolescents with ADHD and ASD+ADHD, on and off stimulant medication, in attention test performance and EEG power spectra. The main results revealed that although behavioral and neuropsychological measures of attention were similar in adolescents with ADHD and ASD+ADHD, absolute theta was elevated in ADHD compared to ASD+ADHD during the eyes open and task conditions, irrespective of stimulant medication use.

In line with the only previous study comparing power spectra in adolescents with ADHD and ASD+ADHD (Clarke et al., 2011), no differences between these groups in terms of absolute theta were observed during an eyes closed condition. Extending the protocol used by Clarke et al. (2011), in which only an eyes closed condition was investigated, we recorded power spectra during an eyes open and a task condition, which revealed overall greater absolute theta in ADHD than in ASD+ADHD. It is notable that in ADHD increased theta power during resting state conditions (Cortese, 2012; Loo & Makeig, 2012; Snyder & Hall, 2006), mainly in frontocentral regions (Loo & Makeig, 2012), was the most robust finding. Theta is associated with an underaroused (Banaschewski & Brandeis, 2007; Loo & Barkley, 2005; Loo & Makeig, 2012) and unfocused state (Loo & Barkley, 2005). It could be suggested that with their eyes open and during the task condition, adolescents with ADHD in the present study were characterized by a more underactive and unfocused state than adolescents with ASD+ADHD. This may indicate that underarousal is a better explanation for attentional problems in adolescents with ADHD than in adolescents with ASD+ADHD; the attentional problems in ASD+ADHD may result from other brain dysfunctions, such as abnormal neuronal connectivity (Billeci et al., 2013; Coben et al., 2008) and top-down processing problems (Gomot & Wicker, 2012), rather than from frontocentral underarousal per se.

It is remarkable that the difference in absolute theta between the diagnostic groups during the eyes open and task conditions was present irrespective of stimulant medication use, because other studies have reported decreased theta and increased beta after stimulant medication use (Clarke et al., 2002; Clarke, Barry, McCarthy, Selikowitz, Brown, et al., 2003; Hermens, Williams, et al., 2005; Loo & Barkley, 2005). However, although stimulant medication partly normalizes theta and beta power, children with ADHD do not reach similar theta and beta levels as TD children (Clarke et al., 2002; Clarke, Barry, McCarthy, Selikowitz, Brown, et al., 2003). Furthermore, the decrease in frontal theta in youngsters with ADHD associated with stimulant medication use has been related to parent-reported behavioral improvement (Loo, Hopfer, Teale, & Reite, 2004). As the adolescents with ASD+ADHD in our study did not show as much absolute theta as adolescents with ADHD, this suggests either that stimulant medication works differently in youngsters with ASD+ADHD or is less effective than in youngsters with ADHD only.

When controlling for overall power, relative theta was similar for both diagnostic groups. Increased relative but not absolute theta, was also seen in youngsters with ASD only (Coben et al., 2008; Murias et al., 2007). In contrast, in youngsters with ADHD both increased relative theta (Chabot & Serfontein, 1996; Clarke et al., 2002; Clarke et al., 1998, 2001a) and increased absolute theta (Cortese,

2012; Loo & Makeig, 2012; Snyder & Hall, 2006) have been reported. Subsequently, it has been suggested that elevated absolute theta is more specific to ADHD than relative theta, the latter being related to ASD as well.

The only difference related to stimulant medication use was that stimulus-medicated adolescents with ADHD showed an increase in total power from anterior to central regions in the eyes open condition, whereas stimulant-medicated adolescents with ASD+ADHD did not. This increase in total power specific to stimulant-medicated adolescents with ADHD during an eyes open condition has not been previously reported. Stimulant medication use is generally associated with decreased total power (Clarke, Barry, McCarthy, Selikowitz, Clarke, et al., 2003), decreased theta and increased beta (Clarke et al., 2002; Clarke, Barry, McCarthy, Selikowitz, Brown, et al., 2003; Hermens, Williams, et al., 2005; Loo & Barkley, 2005). In the current study there were no overall differences in EEG power between stimulant-medicated and stimulant-free adolescents. Baseline differences in age between adolescents on and off stimulant medication in our sample may have contributed to the lack of effects of stimulant medication: the stimulant-free adolescents were, on average, older than stimulant-medicated adolescents. Since aging (Segalowitz, Santesso, & Jetha, 2010) as well as using stimulant medication (Clarke et al., 2002; Clarke, Barry, McCarthy, Selikowitz, Brown, et al., 2003; Hermens, Williams, et al., 2005; Loo & Barkley, 2005) results in decreased theta power, the two effects may have cancelled each other out. In line with the review by Segalowitz et al. (2010) the current study found a clear maturation effect, with older adolescents displaying lower absolute power across all frequency bands, particularly in the posterior region, and increased relative beta. In addition, we observed a maturation effect on attention test performance, with better performance at older ages.

Although increased theta, particularly in the anterior region, is generally thought to be typical of ADHD, we observed an inverse association between posterior theta during the eyes closed condition and performance on the d2 attention test. This finding is similar to that of Hermens, Soei, et al. (2005) who found an inverse correlation between posterior theta during an eyes open condition and reaction time in TD adolescents but not adolescents with ADHD (Hermens, Soei, et al., 2005). It is striking that a lower posterior absolute theta during the eyes open condition was strongly associated with attentional performance in terms of total processed (TN) and total correct processed (C) items in adolescents with ADHD but not adolescents with ASD+ADHD. It should be noted that due to the smaller size of the ASD+ADHD group, associations had to be stronger to reach significance; but taking this difference in sample size into account, the association was so pronounced in the ADHD group that an association of similar strength in the combined ASD+ADHD would have proved significant, as was the association between TN and posterior theta during the eyes closed and task conditions. This finding provides support for the hypothesis that increased theta may be associated with attentional problems in ADHD more often than in ASD+ADHD.

In the current study, lower central absolute beta was associated with improved attention test performance in the adolescents with ADHD. In contrast, in TD young adults an increase in absolute beta during attention test performance has been associated with improved visual attention test performance

(Vazquez Marrufo, Vaquero, Cardoso, & Gomez, 2001). Similarly, strong positive correlations between absolute beta and attention test performance, as well as parent-reported measures of attention in children with ADHD have been reported previously (Loo et al., 2004). The reverse finding - a reduction in absolute beta and improved attention test performance - reflects maturation, which is generally accompanied by a decrease in power across all frequency bands and total power (Segalowitz et al., 2010). In terms of relative beta, the present results did reveal the expected positive association between attention test performance and relative beta in adolescents with ADHD and adolescents with ASD+ADHD.

The current results showed differences in absolute theta activity between adolescents with ADHD and adolescents with ASD+ADHD. Nevertheless, further systematic research on the psychophysiological aspects of ADHD and ASD+ADHD and their implications is warranted. First of all, replication of these psychophysiological results with a larger sample size is needed, ideally with a controlled stimulant medication titration trial including physiological baseline measures with stimulant-free adolescents with ADHD, ASD+ADHD, ASD and TD adolescents. Such a titration trial would control for the baseline differences in stimulant medication use and age that were observed in the current study. Although we controlled for age statistically, it is possible that stimulant medication use and maturation may affect EEG spectra similarly. The stimulant-medicated adolescents in this study were on average younger than the stimulant-free adolescents, this may have concealed potential effects of stimulant medication use. Secondly, the diagnostic group assignments in this study were based on clinician's decisions using DSM-IV (American Psychiatric Association, 2000) criteria; whilst this increased the ecological validity of the study, information about specific diagnostic aspects of ASD were not available. Including diagnostic interviews such as the Autism Diagnostic Interview (Lord, Rutter, & Le Couteur, 1994) or the Autism Diagnostic Observation Schedule (Lord et al., 1989) in future research, could give more detailed information about specific characteristics of ASD. Inclusion of a control group of TD adolescents would make it possible to determine whether physiological patterns in the diagnostic groups differ from those of TD adolescents. Future research should, if possible, include adolescents with ADHD only, ASD+ADHD, ASD only and TD adolescents in order to uncover the physiological patterns associated with ADHD, ASD, ASD+ADHD and typical development.

In conclusion, adolescents with ADHD displayed more absolute theta activity than adolescents with ASD+ADHD with their eyes open and during performance of a task. In addition, adolescents with ADHD but not adolescents with ASD+ADHD showed an association between diminished attention test performance and increased theta with their eyes open. The current study suggests that although there is an overlap in behavioral ADHD characteristics between adolescents with ADHD and adolescents with ASD+ADHD, the underlying psychophysiological mechanisms responsible may be different. This finding may help to explain why stimulant medication is less effective in ASD+ADHD than in ADHD. Further research into the psychophysiology of ASD+ADHD is therefore warranted.

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CHAPTER 4

Auditory ERP components and stimulant medication use in adolescents with ADHD or Autism Spectrum Disorders and comorbid ADHD

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ABSTRACT

The current study explored event-related potentials for an auditory oddball task in adolescents diagnosed with Attention Hyperactivity Deficit Disorder (ADHD; n=33) or autism spectrum disorder with ADHD (ASD+ADHD; n=20) and categorized by stimulant medication use (57% of total sample) to investigate underlying brain functions. There was an interaction between diagnostic group and stimulant use for N1 latency and N2 amplitude, but not for the P3 component. Medication was associated with reduced N1 latencies in ADHD and with prolonged N1 peak latencies in ASD+ADHD. In ASD+ADHD, N2 amplitude was lower in stimulant-free adolescents; in ADHD there were no differences in N2 amplitude associated with stimulant medication. Results suggest that the brain mechanisms underlying attention deficits may differ between these groups.

INTRODUCTION

Features of attention deficit hyperactivity disorder (ADHD), such as hyperactivity/impulsivity symptoms and inattention symptoms, frequently occur in autism spectrum disorders (ASD) (American Psychiatric Association 2013). Estimates of the prevalence of ADHD in ASD range from 28 percent to over 50 percent (Simonoff et al. 2008; Lee and Ousley 2006; Gjevik et al. 2011). Stimulant medication and behavioral therapy are the treatments of choice for reducing ADHD symptoms. Stimulant medication is effective in reducing ADHD symptoms in youngsters with ADHD (Greenhill et al. 2001; Faraone and Buitelaar 2010). However, there are indications that stimulant medication is less effective in youngsters with co-occurring ASD and ADHD (ASD+ADHD) (Cortese et al. 2012; Research Units on Pediatric Psychopharmacology (RUPP) Autism Network 2005). Within the ADHD population, the number of hyperactivity/impulsivity symptoms declines with age (Hart et al. 1995; Kessler et al. 2005) and this is also true for the majority of youngsters with ASD+ADHD, whereas inattention symptoms seem to persist (Lee and Ousley 2006). This persistence makes attention processes in these groups of high clinical interest. It is not clear however, whether ADHD in ASD is similar to ADHD in the absence of ASD; in consequence it is not known whether stimulant medication that seems to treat ADHD effectively (Greenhill et al. 2001; Faraone and Buitelaar 2010) produces comparable effects in ASD+ADHD. Stimulant medication may be less effective in reducing ADHD symptoms in youngsters with ASD and it produces many adverse effects in youngsters with ASD (RUPP 2005; Cortese et al. 2012). Together, these finding indicate that despite the behavioral overlap in attention problems, there may be physiological differences between ADHD and ASD+ADHD. Better understanding of brain functioning related to attention in ADHD and ASD and the effects of stimulant medication may help to explain the different effects of stimulant medication in youngsters with ASD+ADHD and ADHD. Auditory event related potentials (ERPs) during performance of an oddball task are related to attentional processing and may offer insight into the attention deficits in ADHD and ASD+ADHD.

Abnormal ERPs are seen in adolescents with ADHD (Johnstone et al. 2013) and ASD (O'Connor 2012; Gomot and Wicker 2012). ERP components can be related to cognitive functions such as attention, response selection, inhibition, and response monitoring (Johnstone et al. 2013). With regard to attention, a recent review indicated that youngsters with ADHD have problems with stimulus discrimination (N2) and problem evaluation (P3) on oddball tasks, when compared to typical developing (TD) youngsters (Johnstone et al. 2013). Specifically, the N1 amplitude, which is associated with the processing of stimulus characteristics (Näätänen and Picton 1987); the N2, which is associated with stimulus orienting and discrimination (Näätänen et al. 1982); and the P3, which is associated with selective attention and working memory capacity (Polich and Herbst 2000), are abnormal during attentional task performance in youngsters with ADHD (Johnstone et al. 2013; Barry et al. 2003). In youngsters with ADHD, the N1 amplitude was reduced during some developmental stages: in pre-adolescence (age 7 to 9 years) and from middle adolescence (16 years and older) (Barry et al. 2003). In

addition, reduced N1 peak enhancement from non-target to target stimuli has been seen in ADHD (Barry et al. 2003). Other studies have found enlarged N1 amplitude (Johnstone et al. 2013). The findings relating to N2 and P3 amplitudes are more reliable, these components are generally decreased in youngsters with ADHD (Johnstone et al. 2013; Barry et al. 2003). In addition to decreased P3 activity, adolescents with ADHD or conduct disorder show prolonged N2 and P3 latencies (Du et al. 2006). Stimulant medication appears to have some influence on ERPs, as increased P3 (Groom et al. 2010; Hermens et al. 2005) and N2 (Pliszka et al. 2007) amplitudes have been seen in adolescents with ADHD following stimulant medication use.

Youngsters with ASD show abnormal patterns mainly in the earlier N1 and N2 ERP components (O'Connor 2012). Studies of ERP characteristics in ASD have produced mixed results for the early negative components. The N1 amplitude has been found to be attenuated in ASD children (O'Connor 2012). Shorter and longer N1 latencies have been reported (O'Connor 2012). N2 amplitudes range from reduced to normal in ASD (O'Connor 2012). In most research, the later positive P3 amplitude has been reported to be smaller in ASD children than TD children and adolescents (O'Connor 2012; Gomot and Wicker 2012), indicating a deficit in sustained attention to detecting oddball stimuli.

There have been very few direct comparisons of children with ADHD, ASD, and ASD+ADHD, and the data are restricted to visual tasks (Tye et al. 2013a; Gomarus et al. 2009; Kemner et al. 1999; Tye et al. 2013b). In a visual continuous performance task, children with ASD+ADHD and ADHD showed reduced N2 amplitudes compared to TD children (Tye et al. 2013a). In addition, the increase in N2 amplitude from target to no-target trials was smaller in children with ASD and ASD+ADHD compared to children with ADHD and TD children. Children with ADHD showed smaller frontal P3 amplitudes than children with ASD (Kemner et al. 1999) and attenuated P3 to attention orienting cues and inhibition of P3 related non-targets was found in children with ASD+ADHD or ADHD compared to children with ASD or TD children (Tye et al. 2013a). Moreover, children with ASD+ADHD showed a smaller increase in occipital P3 amplitude to target-relevant features than children with ASD, ADHD, or TD children (Gomarus et al. 2009). Overall, these reductions in N2 and P3 may indicate that in children with ASD+ADHD, abnormal ERP patterns are the summation of abnormalities characteristic of ADHD and ASD.

In summary, the current literature suggests that youngsters with ASD show abnormal patterns in the earlier ERP components, whereas in youngsters with ADHD the main abnormality in ERPs is in the later P3 component. Stimulant medication seems to normalize ERPs in adolescents with ADHD, but it is less clear that it produces similar outcomes for adolescents with ASD+ADHD. The aim of the current study was therefore to explore ERP abnormalities in adolescents diagnosed with ADHD or ASD+ADHD. In addition, differences in ERP patterns associated with use of stimulant medication were also explored. It was predicted that (a) adolescents with ASD+ADHD would show similar or reduced N1, reduced N2, and similar P3 when compared with adolescents with ADHD; and

(b) stimulant-medicated adolescents in both groups would show larger ERP amplitudes and shorter latencies than stimulant-free adolescents.

METHOD

Participants

This study used a subsample of 53 adolescents who had been recruited for an intervention study for adolescents with clinical ADHD symptoms. Prior to the start of the study, approval was obtained from the Medical Ethics Committee for Mental Health Institutions in the Netherlands (Ref. no: NL 24776.097.08 CCMO). The study took place in three centers of child and adolescent psychiatry (GGzE, GGz Breburg, Reinier van Arkel group) in the southern part of the Netherlands. Written informed consent was obtained from each participant. Where the participant was younger than 18 years the parents also provided written informed consent. The sample was similar to that used by (Bink et al. 2013), but 5 adolescents were excluded because of the quality of the EEG data and 2 additional patients were included: one who had enrolled later in the study and one for whom no response measures of the oddball task were available.

Two diagnostic groups of male adolescents between 12 and 24 years old were included in the study. The first group consisted of 33 adolescents with a clinical DSM-IV-TR (American Psychiatric Association 2000) primary diagnosis of ADHD: combined subtype (n=16), inattentive subtype (n=16), hyperactive /impulsive subtype (n=1). The second group consisted of 20 adolescents with a primary diagnosis of ASD: Asperger's syndrome (n=6), pervasive developmental disorder – not otherwise specified (PDD-NOS; n=14). Adolescents with ASD also had a notification of clinical ADHD with symptoms sufficient for a clinical diagnosis of ADHD. ADHD symptoms were assessed using a Dutch DSM-IV-based semi-structured ADHD interview for adults (Kooij 2002) and the Mini International Neuropsychiatric Interview (MINI; Sheehan et al. 1997; Sheehan et al. 1998). Exclusion criteria were IQ<80, neurological disorders, schizophrenia and other psychotic disorders, depression, attachment disorder or anxiety disorder, use of cannabis in the 24 hours prior to physiological assessment, use of medication other than stimulant medication.

Stimulant medication use was monitored through an intervention questionnaire based on the Dutch national basic ADHD program for children and adolescents (Vink and Van Wamel 2007). Adherence to prescribed medication was determined by asking the adolescents whether they had been taking their medication as prescribed. In total, 30 (57%) adolescents used stimulant medication. In the ADHD group, 19 (58%) used stimulant medication: 6 used immediate release methylphenidate and 13 used sustained release methylphenidate. In the ASD+ADHD group, 11 (55%) used stimulant medication: 1 used immediate release methylphenidate and 10 used sustained release methylphenidate. Two adolescents in the ASD+ADHD group used low doses (0.5 mg and 1.5 mg per day) of antipsychotic medication (Risperdal®) in addition to their stimulant medication; because the dosage

was low and combined with stimulant medication, we considered that the potential impact on the outcome measures would be minimal.

Comorbid disorders were allowed: included in the ADHD group were participants with substance-related disorders (*n*=2), conduct disorders (*n*=3), and reading disorder (*n*=2), and in the ASD+ADHD group, conduct disorder (*n*=1) and reading disorder (*n*=1).

Outcome measures

Group characteristics

The group characteristics are listed in Table 1. We have reported Global Assessment of Functioning (GAF) score, the DSM-IV based ADHD-rating scale (Kooij et al. 2005; Kooij et al. 2008), the MINI subscales for inattention and hyperactivity/impulsivity (HI), the Autism-Spectrum Quotient (AQ)-adolescent version for individuals with normal intelligence (Baron-Cohen et al. 2006; Baron-Cohen et al. 2001), the Child Behavior Checklist (CBCL) and the Youth Self Report (YSR;(Achenbach 1991), and the WISC-III or the WAIS-III (Wechsler 1991, 1997) full-scale total intelligence quotient (TIQ). Further information about the reported group characteristics can be found elsewhere (Bink et al. 2013).

Auditory oddball task

The auditory oddball task is an attention test in which relevant target stimuli need to be processed and irrelevant standard stimuli need to be ignored. In this task a 75dB tone lasting 50 ms was presented binaurally by headphones every second. Low frequency standard tones (500Hz) were presented 280 times and intermixed with infrequent (60 presentations in 6 minutes) high target tones (1000Hz); the tones were presented in quasi-random order. The duration of both standard and target tones was 5ms. Adolescents were asked to press the answer box with both index fingers as fast as they could on hearing the high frequency 1000Hz target tone. Hearing ability for the different tones was checked in a short practice trial before the start of the oddball task. Response measures included mean reaction time, reaction time variability and total number of errors.

Psychophysiological recording

Electroencephalograms (EEGs) were recorded between 10am and 11am. When applicable, stimulant medication was taken during breakfast, before the measurement. No caffeine or nicotine intake was allowed in the two hours prior to physiological assessment.

The EEG-recording was performed in combination with a subset of the brain resource company (BRC, Ultimo, Australia) test battery. This included a baseline condition in which adolescents had to sit quietly with their eyes closed for two minutes. Subsequently they performed the task condition, which consisted of a six-minute auditory oddball task. EEGs were recorded according to the 10-20 system using a Quick-Cap with 26 EEG channels. Horizontal electrooculograms (EOGs)

were recorded with two electrodes placed 1.5cm lateral to the canthi of the eyes. Vertical EOGs were recorded with electrodes placed above and below the middle of the eye with the upper electrode placed 3mm above the eyebrow and the other electrode 1.5cm below the lower eyelid. A Neuroscan NuAmps amplifier recorded the signals with a sampling rate of 500Hz, a 100Hz low pass anti-aliasing filter and 32-bit DC high-pass filter,.

EEG recordings were analyzed with a Brain Vision Analyzer v2.0 (Brain Products GmbH, Germany). References were set offline to linked mastoid; a 0.5Hz 12dB/oct high pass filter, and a 30Hz, 48dB/oct low pass filter were applied. Ocular correction was applied according to the procedure of Gratton et al. (1983). Automatic raw data inspection was applied with a maximum allowed voltage step of 50μV/ms, maximum allowed interval difference of 200μV, and minimum and maximum allowed amplitudes of -200μV and 200 μV respectively. Data was marked as bad 200ms before and after the event; the lowest permitted level of activity in intervals was 0.5μV with an interval length of 100ms. Data was segmented from 100ms pre-stimulus to 500ms post-stimulus, and the 100ms pre-stimulus interval was used for baseline correction. We used automatic artifact rejection inspection in each segment with a maximum voltage step of 50μV/ms, maximum allowed difference in intervals of 100μV, minimum allowed amplitude of -100μV, maximum allowed amplitude of 100μV, and the lowest permitted level of activity in the 100ms intervals was 0.5μV. Averages over all the segments were calculated separately for standard and target tones and for each channel. Semi-automatic peak picking was based on the target, with the N1 at 50-150ms, the N2 at 150-250ms and the P3 at 250–500ms. Peaks were inspected visually by the first author (MB), who was blind to diagnostic group and stimulant medication use, and were manually adjusted if necessary. Peak picking was not done separately for the standard wave, because it was not feasible to score the N2 and P3 components reliably due to the shape of the standard wave. To address the standard wave, difference waves were calculated as the difference between the target and standard stimuli at the moment of the observed target peak. Peak amplitudes were assessed as the mean value in μV of a 10ms interval around the peak, and for each channel peak latencies in ms were exported to SPSS.

Initial regions of interest (ROIs) were based on a principal component analysis (PCA) of the target N1, N2 and P3 peak amplitudes (V) with covariance matrix, varimax rotation, and Kaiser normalization. Missing values (1.23%) were replaced using mean imputation. Three ROIs were distinguished: anterior, central and posterior. For an electrode to be included, the electrode had to be part of the same ROI for all three components: N1, N2 and P3. Three congruent ROIs were distinguished for 16 electrodes: anterior [Fp1, Pp2, F7, F3, Fz, F4, F8,], central [C3, Cz, C4,], and posterior [P3, Pz, P4, O1, Oz, O2]. Accordingly, ROI values were calculated for the N1, N2, and P3 components as the means of values at the relevant electrodes.

Data quality did not differ between the diagnostic groups or with stimulant medication use. Total included electrodes, M=15.85, SD=.60, did not differ between the diagnostic groups, $F(1,51)=2.01$, $\eta p^2=.04$, $p>.05$, or with stimulant medication use, $F(1,51)=1.37$, $\eta p^2=.03$, $p>.05$. For

standard and target stimuli the number of artifact free segments of the electrode with the fewest included segments (minimum segments) was considered. The mean number of minimum segments for standard stimuli, M=271.55 SD=14.36, and target stimuli, M=57.00, SD=5.27, did not vary across the diagnostic groups (standard: $F(1,51)=.09$, $\eta p^2=.00$, $p>.05$; target: $F(1,51)=.03$, $\eta p^2=.00$, $p>.05$) or with stimulant medication use (standard: $F(1,51)=.01$, $\eta p^2=.00$, $p>.05$; target: $F(1,51)=.02$, $\eta p^2=.00$, $p>.05$).

Data analysis

All analyses were performed using SPSS version 19.0. Differences in group characteristics were analyzed with a one-way ANOVA or a chi-square test ($\chi 2$) with Fisher's exact correction. Generalized Linear Model (GLM) repeated-measures (RM) ANCOVAs were conducted separately for the peak amplitudes and latencies, with age as covariate, ROI as within-subjects factor and diagnostic group (ASD+ADHD or ADHD) and stimulant use (stimulant-medicated and stimulant-free) as between-subjects factors. The full factorial models were tested. All ROI effects were evaluated using multivariate test criteria, a method known to be robust against violations of sphericity (Vasey and Thayer 1987). Effect sizes have been expressed as percentage of explained variance in partial $\eta 2$ (η_p^2). In addition, the adjusted difference between ROIs (AD) and 95% confidence interval [95% CI] have been reported where applicable. Significant two-way between-groups interactions were explored with post hoc GLM RM ANCOVA for diagnostic group, with age as covariate, ROI as within-subjects factor and stimulant medication use as between-subjects factor. Pearson correlations for all latency and amplitude measures were calculated for all ERP components. In addition, where there was a main effect of diagnostic group or stimulant medication on an ERP component, Pearson's correlation coefficients for reaction time and reaction time variability were considered separately for each diagnostic group and stimulant medication use group as well as for the whole sample.

Values of $p<.05$ were considered statistically significant; $p<.10$ was considered a trend. Only significant results and trends have been reported. Because of the exploratory nature of the study, no alpha correction for multiple testing was applied. Effect sizes have been expressed as percentage of explained variance in partial $\eta 2$ (η_p^2).

RESULTS

Group characteristics

There were no differences between the diagnostic groups (ADHD, ASD+ADHD) in terms of age, M=15.42 years, SD=2.88, or stimulant medication use, $\chi 2(1, 51)=.00$, $p>.05$. In addition, the mean prescribed dose for stimulant-medicated adolescents was similar in the ADHD group, N=19, M=34.74, SD=13.02, and the ASD+ADHD group, N=11, M=35.27, SD=17.35; $F(1,28)=.01$, $p>.05$, $\eta_p^2=.00$. However, the average age of the stimulant-free adolescents (ADHD: M=16.21 years, SD=3.87; ASD+ADHD: M=16.78 years, SD=2.54) was somewhat older than stimulant-medicated adolescents (ADHD: M=14.63 years, SD=2.19; ASD+ADHD: M=14.64 years, SD=2.38).

Table 1. Group Characteristics.

	TOTAL	ASD+	ADHD	F	η_p^2	Stimulant-medicated	Stimulant-free	F	η_p^2
	n=53	*n*=20	*n*=33			*n*=30	*n*=23		
	Mean (SD)	Mean (SD)	Mean (SD)			Mean (SD)	Mean (SD)		
Age in Years	15.42(2.88)	15.60(2.62)	15.30(3.07)	.13	.00	14.63(2.22)	16.43(3.36)	5.52*	.10
GAF score	55.11(6.45)	54.50(6.10)	55.48(6.73)	.29	.01	55.00(6.65)	55.26(6.33)	.02	.00
AQ-adolescent version[1]	25.58(8.02)	32.45(5.36)	21.41(6.33)	42.35***	.45	24.63(8.10)	26.80(7.93)	.95	.02
ADHD rating scale[2]									
Inattention	4.75(2.24)	4.90(2.25)	4.67(2.26)	.13	.00	4.47(2.22)	5.13(2.24)	1.15	.02
H/I	3.45(1.89)	3.70(2.06)	3.30(1.79)	.55	.01	3.73(1.96)	3.09(1.76)	1.54	.03
Childhood Inattention	6.04(2.67)	5.65(2.83)	6.27(2.58)	.67	.00	6.07(2.68)	6.00(2.71)	.01	.00
Childhood H/I	4.94(2.78)	4.20(2.75)	5.39(2.75)	2.35	.04	5.10(2.80)	4.74(2.82)	.22	.00
MINI ADHD Inattention	5.38(2.48)	5.00(2.53)	5.61(2.46)	.74	.01	5.27(2.50)	5.52(2.50)	.14	.00
MINI ADHD H/I	3.72(2.26)	3.60(2.39)	3.79(2.22)	.08	.00	3.80(2.14)	3.61(2.46)	.09	.00
CBCL Total Problems	62.57(28.89)	72.95(28.27)	56.27(27.81)	4.42*	.08	59.63(26.08)	66.39(32.39)	.71	.01
Internalizing Problems	14.47(9.54)	17.55(10.37)	12.61(8.62)	3.51	.06	13.00(7.71)	16.39(11.39)	1.67	.03
Externalizing Problems	18.79(11.53)	21.80(11.06)	16.97(11.59)	2.24	.04	17.80(10.68)	20.09(12.68)	.51	.01
Attention Problems	11.83(3.50)	12.80(3.62)	11.24(3.34)	2.55	.05	11.87(3.30)	11.78(3.81)	.01	.00
YSR Total Problems	47.42(20.58)	54.30(21.43)	43.24(19.18)	3.79	.07	46.03(17.47)	49.21(24.35)	.31	.01
Internalizing Problems	9.17(5.79)	10.90(6.09)	8.12(5.43)	2.97	.06	8.70(5.33)	9.78(6.42)	.45	.01
Externalizing Problems	15.51(9.66)	17.85(9.89)	14.09(9.38)	1.92	.04	14.97(9.04)	16.22(10.57)	.22	.00
Attention Problems	9.26(3.14)	8.85(3.59)	9.52(2.87)	.55	.01	9.10(2.89)	9.48(3.50)	.19	.00
TIQ	101.83(10.74)	104.90(11.60)	99.97(9.90)	2.71	.05	102.53(11.75)	100.91(9.44)	.29	.01

Note: Data are means (SD); df (1,51); *p<.05, **p<.01, ***p<.001;1 Global Assessment of Functioning score (GAF-score), 2 Autism Spectrum Quotient (AQ) – adolescent version is a parent report; 3 The ADHD rating subscales are retrospective self-reported current and childhood symptoms

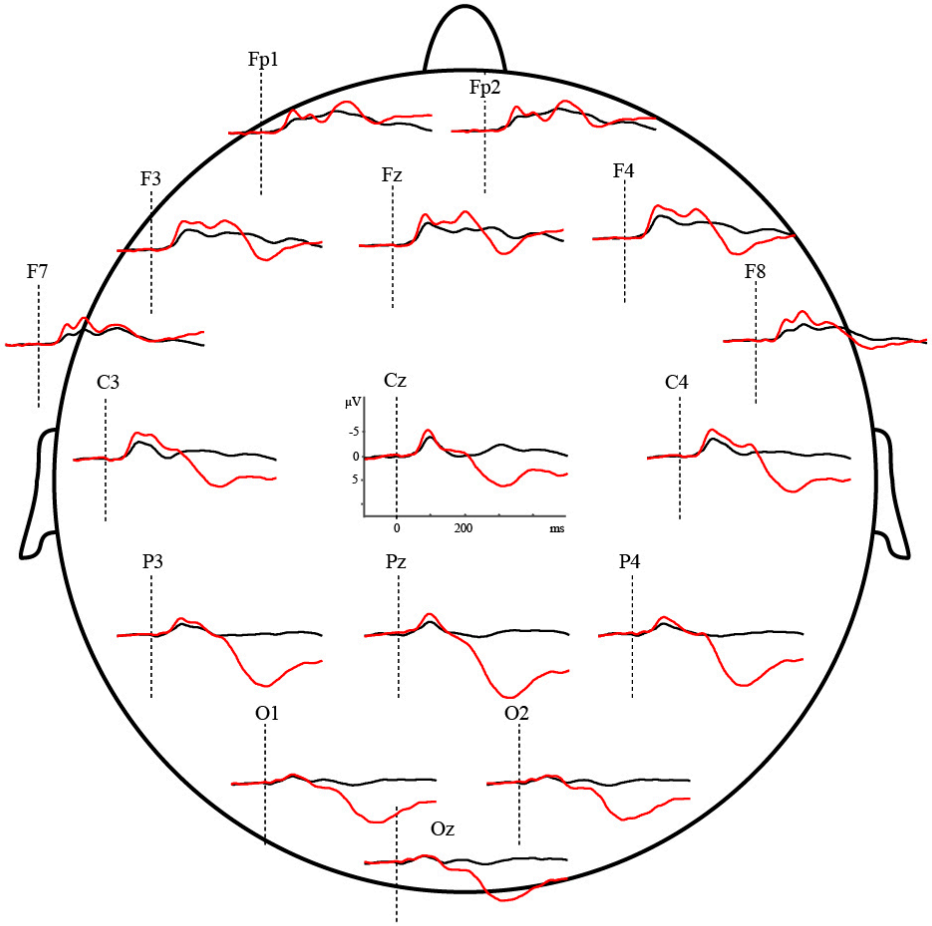
This age difference was similar for the ADHD group and the ASD+ADHD group, $F(3,49)=.12$, $p>.05$, $\eta_p^2 =.00$. Stimulant-free and stimulant-medicated adolescents did not differ significantly on other group characteristics.

The AQ-adolescent version confirmed that the ASD+ADHD group exhibited more symptoms of autism than the ADHD group. The parents of the ASD+ADHD group reported more behavioral problems on the CBCL. The diagnostic groups did not differ on other group characteristics.

ERPs

The peak amplitude, difference wave and latency measures of the ERP components are summarized in Table 2. Figure 1 depicts the topographical distribution of the grand averages of the standard, target and difference waves.

Figure 1. *Topographical distribution of ERP activity*



Note: Grand averages for the whole sample are depicted. The black line represents the standard wave, the red line the target wave. For graphical presentation of the ERPs, electrode positions are slightly adapted from the original electrode position. Original electrode positions are according to the 10-20 system

Diagnostic group and stimulant medication use

The N1 peak latencies showed an interaction between diagnostic group and stimulant medication use. Post hoc separate analysis of the diagnostic groups revealed that stimulant-medicated adolescents with ASD+ADHD had longer N1 peak latencies than stimulant-free adolescents with ASD+ADHD, $AD_{ASD+ADHD\ (stimulant\text{-}medicated)\text{-}(stimulant\text{-}free)}$ [95%CI]=17.47[5.65-29.29], F(1,17)=9.73, p<..01, η_p^2=.36. In contrast, N1 peak latencies were shorter in stimulant-medicated adolescents with ADHD than stimulant-free adolescents $AD_{ADHD\ (stimulant\text{-}medicated)\text{-}(stimulant\text{-}free)}$ [95%CI]= 9.78[-19.07--.50], F(1,30)=4.63, p<.05, η_p^2=.13. Representative grand averages are depicted in Figure 2.

There was an interaction between diagnostic group and stimulant use for the N2 peak amplitude and N2 difference wave. Post hoc separate analysis of the diagnostic groups confirmed that stimulant-free adolescents with ASD+ADHD had lower N2 peak amplitudes than stimulant-medicated adolescents with ASD+ADHD for the target peak: $AD_{ASD+ADHD\ (stimulant\text{-}medicated)\text{-}(stimulant\text{-}free)}$ [95%CI]=-4.37 [-8.09--.65], F(1,17)=6.16, p<.05, η_p^2=.27 and for the difference wave: $AD_{ASD+ADHD(stimulant\text{-}medicated)\text{-}(stimulant\text{-}free)}$ [95%CI]=-4.02 [-7.90--.15], F(1,17)=4.80, p<.05, η_p^2=.22. In the ADHD group there was no significant difference in N2 peak amplitude between stimulant-free and stimulant-medicated adolescents for the target peak: $AD_{ADHD\ (stimulant\text{-}medicated)\text{-}(stimulant\text{-}free)}$ [95%CI]=1.06 [-1.55-3.67], F(1,30)=.69, p>.05, η_p^2=.02 or the difference wave: $AD_{ADHD\ (stimulant\text{-}medicated)\text{-}(stimulant\text{-}free)}$ [95%CI]=.99 [-1.63-3.62], F(1,30)=.60, p>.05, η_p^2=.02. Representative grand averages are depicted in Figure 3.

There were no significant interactions for the P3 peak amplitude or difference wave. For the P3 latency there was a trend towards an interaction between diagnostic group and stimulant medication use. Post hoc separate analyses of the P3 latency for each diagnostic group did not confirm a trend for stimulant-free and stimulant-medicated adolescents to differ in P3 in either group.

Age effects

Effects of age and interactions between age and scalp distributions of the ERP components are summarized in Table 2. Age was taken into consideration because the stimulant-medicated adolescents were on average younger than stimulant-free adolescents.

Overall, the N1 peak latencies were shorter for older adolescents than younger adolescents, F(1,48)=4.31, p<.05, ηp2=.08.

Scalp distribution of the N2 interacted with age. The older adolescents showed less negative N2 peak amplitudes than the younger adolescents at anterior, B=.68, p<.005, but not central, B=.10, p>.05, or posterior, B=-.04, p>.05 regions. Accordingly, the difference wave of the N2 was also less negative at anterior, B=.68, p<.005 but not central, B=.05, p>.05, or posterior, B=-.08, p>.05 regions. In addition, there was a trend for scalp distributions of the N2 latency to interact with age, with a trend for shorter N2 latencies at posterior, B=-2.40, p=.06, but not central, B=-.20, p>.10 or anterior, B=-.67, p>.10 locations.

There was a trend for scalp distributions of the P3 peak amplitude to interact with age. The P3 peak amplitude was less positive in older than younger adolescents at posterior sites, B=-.63, p<.05, there was a trend towards this pattern centrally, B=-.46, p=.09, but no age difference at anterior sites, B=.06, p>.05.

Topographical distribution

The N2 and P3 peak amplitudes and difference waves exhibited characteristic scalp distributions (see Table 2).

The N2 peak amplitude was more negative at anterior than central sites, $AD_{anterior\text{-}central}$ [95%CI]=-3.25 [-4.39--2.11]; more negative at central than posterior sites, $AD_{central\text{-}posterior}$ [95%CI]=-3.35 [-4.44--2.27] and also more negative at anterior than posterior sites, $AD_{anterior\text{-}posterior}$ [95%CI]=-6.60 [-7.91--5.29]. The N2 difference wave was not significantly more negative at anterior sites than central sites, $AD_{anterior\text{-}central}$ [95%CI]=-.91 [-2.10, .28]; but was more negative at central than posterior sites, $AD_{central\text{-}posterior}$ [95%CI]=- 3.54 [-4.56--2.51] and more negative at anterior than posterior sites, $AD_{anterior\text{-}posterior}$ [95%CI]=-4.44 [-5.77--3.12].

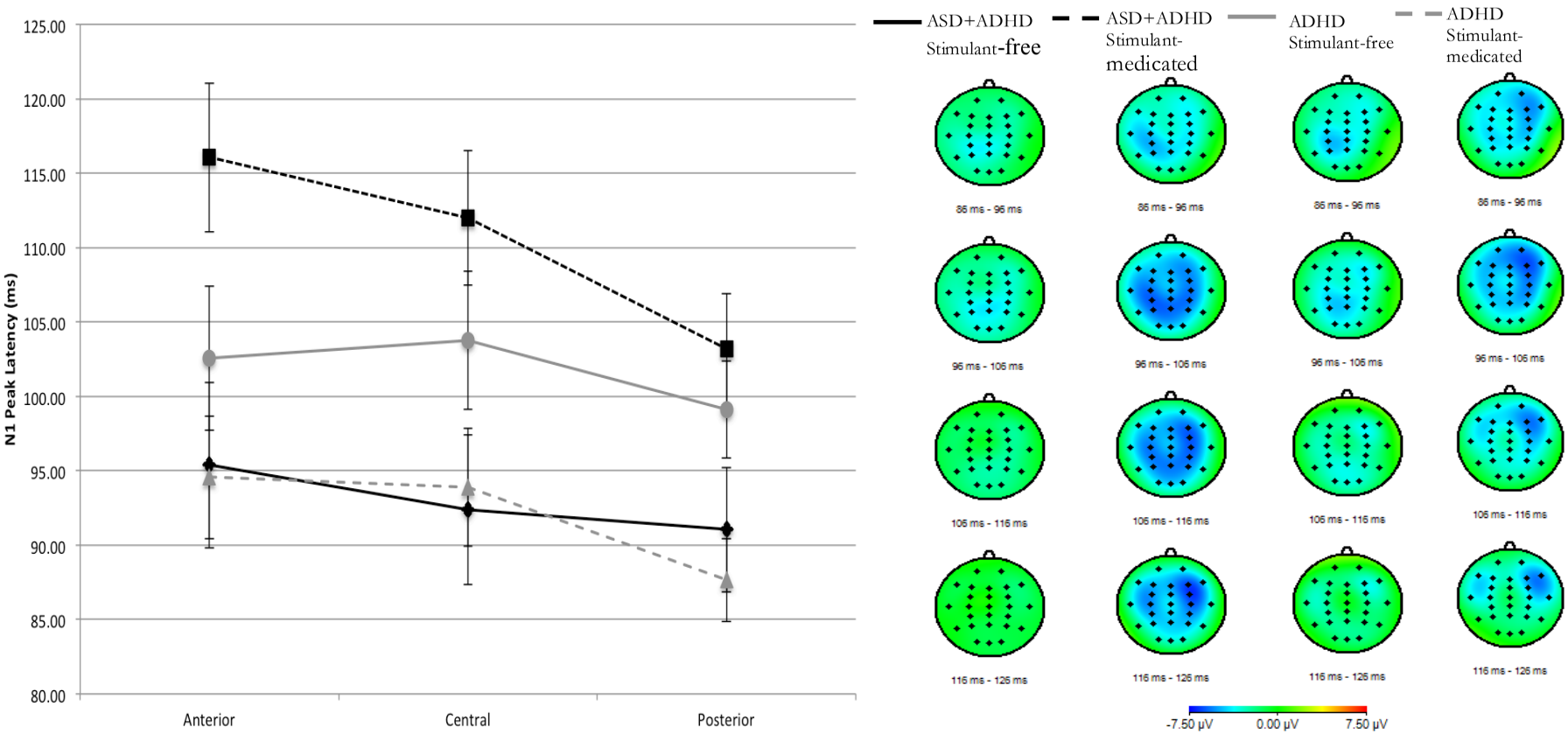
The P3 peak amplitude was more positive at posterior sites than central sites, $AD_{posterior\text{-}central}$ [95%CI]=2.32 [1.14-3.50]; more positive at central than anterior sites, $AD_{central\text{-}anterior}$ [95%CI]=6.56 [5.27-7.84] and more positive at posterior than anterior sites, $AD_{posterior\text{-}anterior}$ [95%CI]=8.88[7.27-10.49]. The P3 difference wave was more positive at posterior sites than central sites, $AD_{posterior\text{-}central}$ [95%CI]=1.89 [.72-3.05]; more positive at central than anterior sites, $AD_{central\text{-}anterior}$ [95%CI]=5.78 [4.52-7.03] and more positive at posterior than anterior sites, $AD_{posterior\text{-}anterior}$ [95%CI]=7.66 [6.04-9.28].

Table 2. GLM RM ANCOVA of Auditory Oddball ERP Peak by Diagnostic Group and Medication Use, with Age as Covariate.

	Anterior	Central	Posterior	AGE		GROUP		MED		GROUP*MED		ROI		ROI*AGE	
	Mean(SD)	Mean(SD)	Mean(SD)	F	η_p^2	F	η_p^2	F	η_p^2	F	η_p^2	F	η_p^2	F	η_p^2
Peak Amplitude Target (μV)															
N1	-6.68 (3.48)	-6.85 (3.70)	-3.74 (2.06)	.78	.02	.29	.01	1.65	.03	1.38	.03	.50	.02	.11	.00
N2	-7.56 (4.46)	-4.27 (5.24)	-.74 (3.58)	1.84	.04	.80	.02	1.73	.04	4.97*	.09	11.98***	.34	5.44**	.19
P3	2.37 (3.94)	9.02 (5.16)	11.56 (5.36)	2.89†	.06	.34	.01	.49	.01	.64	.01	10.18***	.30	3.19†	.12
Peak Amplitude Difference Wave (μV)															
N1	-5.15 (3.59)	-5.49 (3.72)	-3.77 (2.24)	1.85	.04	.27	.01	1.89	.04	2.07	.04	.02	.00	.17	.01
N2	-6.82 (4.47)	-5.88 (5.25)	-2.16 (3.61)	1.39	.03	.76	.02	1.41	.03	4.16*	.08	9.40***	.29	5.71**	.20
P3	3.80 (3.97)	9.69 (5.08)	11.76 (5.34)	2.76	.05	.27	.01	.51	.01	.65	.01	8.94***	.28	3.11	.12
Peak Latency (ms)															
N1	101.28 (18.60)	100.00 (17.74)	94.48 (13.89)	4.31*	.08	2.27	.05	.18	.00	6.83*	.12	.11	.00	.39	.02
N2	216.27 (28.89)	200.62 (29.45)	198.05 (25.09)	.75	02	.85	.02	.21	.00	.01	.00	2.75†	.10	2.64†	.10
P3	332.28 (30.93)	333.74 (56.76)	327.60 (38.53)	1.22	.02	.11	.00	.03	.00	3.07†	.06	1.55	.06	1.24	.05

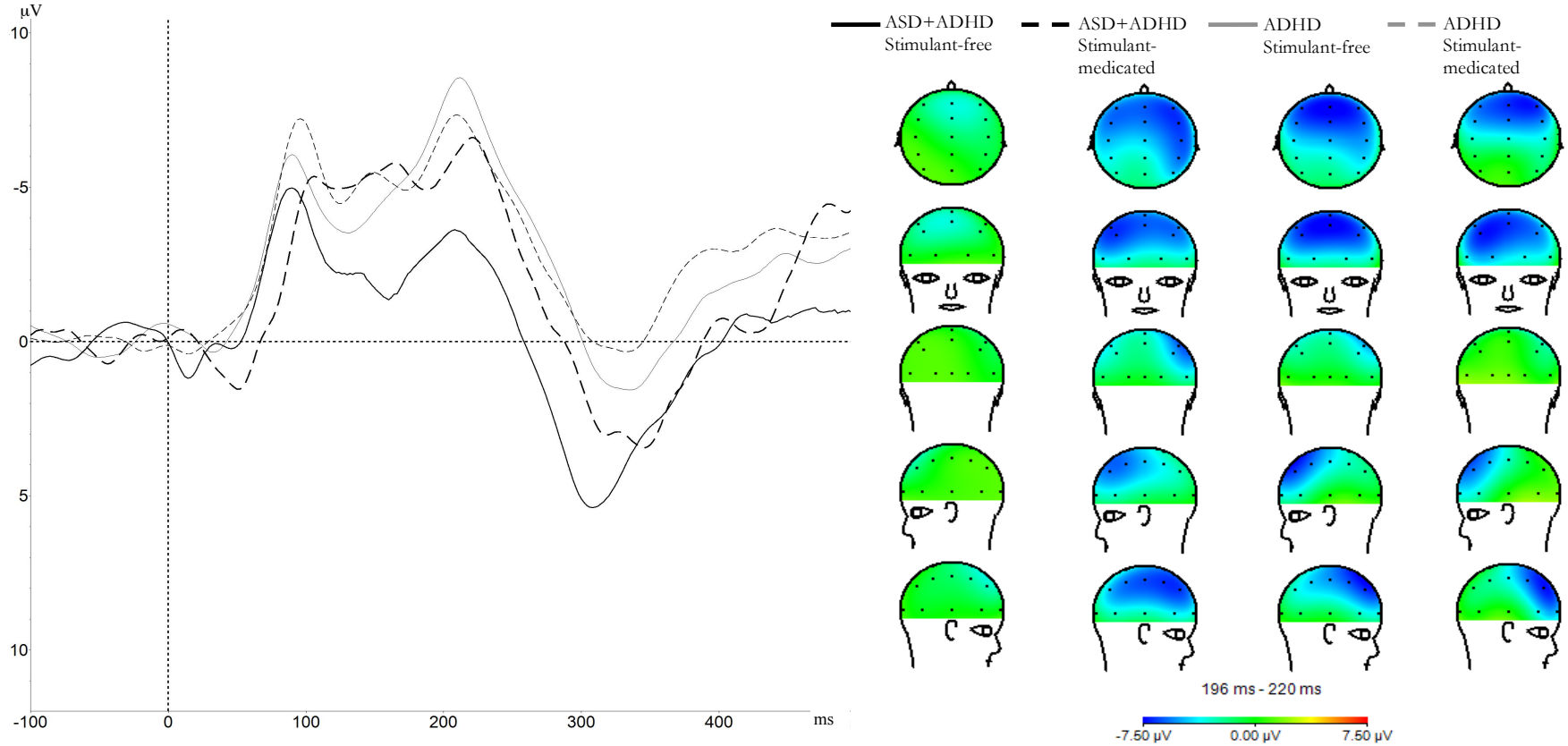
Note: †p<.10, *p<.05, **p<.01, ***p<.001; Data presented are Mean(SD); df (1,48) for age [AGE], diagnostic group [GROUP], stimulant medication use [MED] and the interaction of GROUP and MED; df (2,47) for regions of interest [ROI] and the interaction of ROI and age [AGE];. There were no effects for diagnostic group (ASD+ versus ADHD) or stimulant medication use (Stimulant-medicated versus stimulant-free).

Figure 2. *Interaction between diagnostic group and stimulant medication use for N1 peak latency*



Note Figure 2: The left panel displays estimated marginal means for the N1 peak latency (ms) with standard error bars for each ROI with the evaluated covariate age 15.42 years, separately for stimulant-free and stimulant-medicated adolescents with ASD+ADHD and for stimulant-free and stimulant-medicated adolescents with ADHD. The right panel shows the topographical distribution of grand averages per group for four time intervals – from top to bottom – :86-96ms, 96-106ms, 106-116ms, and 116-126ms. The topographical distributions of the grand averages indicated differences between stimulant-free and stimulant-medicated adolescents. There was an interaction between diagnostic group and stimulant medication use for the N1 peak latency: stimulant-medicated adolescents with ASD+ADHD showed longer N1 peak latencies than stimulant-free adolescents with ASD+ADHD, whereas in adolescents with ADHD, N1 peak latencies were reduced in the stimulant-medicated subgroup.

Figure 3. *Interaction between diagnostic group and stimulant medication use for N2 peak amplitude*



Note: The left panel depicts grand average ERPs at Fz for the stimulant-free adolescents with combined ASD+ADHD (*n=9*), stimulant-medicated adolescents with ASD+ADHD (*n=11*) stimulant–free adolecents with ADHD (*n=14*) and stimulant-medicated adolescents with ADHD (*n=19*). ERP activity is displayed on the y-axis in µV; negative up and positive down as a function of time in ms on the x-axis. The right panel depicts the topographical distributions of grand averages in the N2 time interval for each group from 196- 220ms. There was an interaction between diagnostic group and stimulant medication use for the N2 peak amplitude. Stimulant-free adolescents with ASD+ADHD showed diminished N2 peak amplitude compared to stimulant-medicated adolescents with ASD+ADHD, whereas there was no difference between stimulant-free and stimulant-medicated adolescents with ADHD for N2 peak amplitudes.

Amplitude and latency correlations

Correlations between latencies and amplitude for the three components are summarized in Table 3. There was a negative correlation between N1 latency and peak amplitude at anterior and posterior sites: longer latencies correlated with more negative (i.e. larger) N1 peak amplitudes. Similar, N1 latencies correlated negatively with N1 difference waves at anterior, central and posterior sites. Latencies and peak amplitudes or difference waves were not correlated for the N2 and the P3 components of the ERP.

Table 3. Correlation Between Latency and Amplitude Measures.

		Latency		
		Anterior	Central	Posterior
Peak Amplitude Target	**N1**	*-.390***	-.209	*-.302**
	N2	-.068	.038	-.060
	P3	-.033	-.178	-.124
Peak Amplitude Difference Wave	**N1**	*-.437**	*-.306**	*-.557***
	N2	-.035	.026	-.056
	P3	-.034	-.158	-.105

Note: *p<.05, **p<.01; Pearson's correlations between latency and amplitude (peak amplitude and difference waves) of the same ROI (Anterior, Central or Posterior) for each of the three ERP components (N1, N2 and P3)

ERP activity related to task performance

There were no significant correlations between reaction time or reaction time variability and N2 peak amplitude or N2 difference wave. Reaction time was not correlated with N1 latencies. Variability in reaction time was negatively correlated with N1 latency at anterior and central sites (Table 4). Over the whole sample, long latencies were related to low reaction time variability. Considering the diagnostic groups separately, long anterior and central N1 latencies were related to low reaction time variability for adolescents with ASD+ADHD, but there was no significant relationship in adolescents with ADHD. In addition, for stimulant-medicated adolescents long central N1 latencies were associated with low reaction time variability. In stimulant-free adolescents long posterior N1 latencies were associated with low reaction time variability.

Table 4. Correlation Between Latency and Variability in Reaction Time.

Reaction Time	TOTAL	ASD+ ADHD	ADHD	Stimulant-medicated	Stimulant-free
Variability	*n* =53	*n*=20	*n*=33	*n*=30	*n*=23
N1 peak latency					
Anterior	-.315*	-.463*	-.211	-.328	-.302
Central	-.347*	-.523*	-.239	-.403*	-.318
Posterior	-.140	-.332	-.014	.129	-.442*

Note: *p<.05, **p<.01; Pearson correlations between N1 latency and reaction time variability.

DISCUSSION

The current study explored ERPs in stimulant-medicated and stimulant-free adolescents diagnosed with ADHD or ASD+ADHD. To our knowledge, there are no other published ERP studies that included stimulant-medicated adolescents with a diagnosis of ASD+ADHD. The results of this study showed that stimulus processing, reflected in N1 latencies and N2 peak amplitudes, is different in adolescents with ADHD and adolescents with ASD+ADHD, both on and off stimulant medication.

The current study did not reveal overall ERP differences between ADHD and ASD+ADHD. These results are in line with the study of Gomarus et al. (2009), which also failed to differentiate between stimulant-free children with ADHD, ASD or ASD+ADHD in terms of early visual ERPs – up to 300 s – or behavioral measures related to selective attention. However, Tye et al. (2013a) did find that the reduction in N2 amplitude enhancement for non-target stimuli was different in ADHD and ADHD+ASD. On the basis of earlier studies we predicted overall differences for the N1 and N2 components between the two diagnostic groups. Stimulant-medication may modulate these overall effects. In the current study these early negative components were differently affected by stimulant medication in adolescents with ADHD and ASD+ADHD.

For adolescents with ASD+ADHD N1 peak latencies were longer under stimulant medication than stimulant-free. The opposite pattern was observed for the adolescents with ADHD; N1 peak latencies -were shorter in stimulant-medicated than in stimulant-free adolescents. Shorter latencies are generally seen as an indication of more efficient information processing. Nonetheless, the results of the current study also showed that prolonged central N1 latencies were associated with more negative (larger) N1 amplitudes. In addition, long N1 latency was related with less reaction time variability, mainly in adolescents with ASD+ADHD. These results suggest that the later N1 peak is associated with a more consistent reaction to target stimuli.

In adolescents with ASD+ADHD, the N2 peak amplitudes and difference waves were smaller stimulant-free than under stimulant medication, but no such difference was found for adolescents diagnosed with ADHD. The smaller N2 difference wave suggests that stimulant-free adolescents with ASD+ADHD might have more problems discriminating between standard and target stimuli than stimulant-medicated adolescents with ASD+ADHD. Tye et al. (2013a) found diminished N2 enhancement in target trials in stimulant-free children with ASD or ASD+ADHD than in stimulant-free ADHD or TD children. Both this study and our results indicate that ASD is associated with problems in shifting attention from one stimulus to another. The N2 difference wave in adolescents with ASD+ADHD was larger in stimulant-medicated than stimulant-free adolescents, which may imply that stimulant medication helps to improve stimulus discrimination.

The results of Tye et al. (2013a) indicated that children with ADHD and ASD+ADHD showed more reaction time variability and attenuated P3 amplitudes compared with TD children or children with ASD (Tye et al. 2013a). Previous studies found a normalization of P3 activity in young adolescents with ADHD who were taking stimulant medication (Groom et al. 2010; Hermens et al.

2005). Although a previous investigation with this sample did find improved task performance and less reaction time variability in stimulant-medicated than stimulant-free adolescents (Bink et al. 2013), in line with Groen et al. (2008), we did not find that use of stimulant medication enhanced P3 activity.

Older adolescents showed a shorter N1 latency and smaller anterior N2 peak amplitude and difference wave than younger adolescents. In addition, there was a trend towards shorter posterior N2 latencies and attenuated posterior P3 peak amplitudes in older adolescents. In a healthy population, increasing age is associated with reduced N1 and N2 amplitudes and latencies (Johnstone et al. 1996), although P3 peak amplitudes increase and P3 latencies decrease with age, from childhood to adulthood (Segalowitz et al. 2010; Johnstone et al. 1996). The reduction of N1 peak latencies and anterior N2 amplitudes seen in older adolescents in the current study is in line with the normal developmental trajectory. In contrast, the trend towards age effects on P3 peak amplitudes suggests a variation from typical development.

The current outcomes suggest that use of stimulant medication has different outcomes in ADHD and ASD+ADHD; however, additional research is necessary. Firstly, replication of these results in a larger sample is needed, preferably in the form of a controlled trial titrating dosage of stimulant medication and including EEG measures taken pre-intervention without any form of medication, and at the end of the stimulant medication titration trial. In the current study, adolescents took stimulant medication as prescribed by their physician on the day of assessment, in consequence we were not able to control for initial differences between stimulant-medicated and stimulant-free adolescents such as the ages difference we observed (stimulant-medicated adolescents were somewhat younger than stimulant-free adolescents). Although we controlled for age effects statistically, it is possible that stimulant medication use and maturation produce similar physiological changes; this might have masked potential effects of stimulant medication use in our study. Secondly, the constitution of the diagnostic groups could be improved. Inclusion criteria for the current study were based on the presence of severe ADHD symptomatology and clinical, DSM-IV-based diagnoses made by experts in the participating institutions. Although this increased the ecological validity of the study, more detailed information about the features of ASD is lacking. Future research should therefore entail completion of either the Autism Diagnostic Interview (Lord et al. 1994) or the Autism Diagnostic Observation Schedule (Lord et al. 1989). In addition, because the current study did not include a group of TD adolescents it was not possible to determine whether any of the physiological patterns we observed deviated from those expected in typical development. To determine whether specific physiological patterns are characteristic of ADHD, ASD, ASD+ADHD, and typical development, future research should include TD and ASD-only adolescents as well as adolescents with ADHD and ASD+ADHD.

In conclusion, the present study found smaller N2 amplitudes for stimulant-free adolescents with ASD+ADHD than stimulant-medicated adolescents with ASD+ADHD. This finding suggests that in adolescents with ASD+ADHD stimulus discrimination is better when taking stimulant medication than when stimulant-free. In addition, in adolescents with ASD+ADHD, use of stimulant

medication was associated with longer N1 latencies. In contrast, in ADHD use of stimulant medication was associated with shorter N1 latencies. The current study has shown differences in ERP activity in stimulant-medicated and stimulant-free adolescents with ASD+ADHD compared to adolescents with ADHD. Overall, the results indicate that stimulant medication may affect adolescents with ASD+ADHD differently from adolescents with ADHD. The clinical implications of these physiological differences in response to stimulant medication use should be further investigated to optimize treatment of ADHD in ASD patients.

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CHAPTER 5

Behavioral effects of Neurofeedback in Adolescents with ADHD: A Randomized Controlled Trial

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ABSTRACT

Objective*:* Neurofeedback has been proposed as a potentially effective intervention for reducing Attention Deficit Hyperactivity Disorder (ADHD) symptoms. However, it remains unclear whether neurofeedback is of additional value to treatment as usual (TAU) for adolescents with clinical ADHD symptoms. **Method**: Using a multicenter parallel-randomized controlled trial design, adolescents with ADHD symptoms were randomized to receive either a combination of TAU and neurofeedback (NFB+TAU, *n*=45) or TAU-only (*n*=26). Randomization was computer-generated and stratified for age group (ages 12 through 16, 16 through 20, 20 through 24). Neurofeedback treatment consisted of approximately 37 sessions of theta/sensorimotor rhythm (SMR)-training on the vertex (Cz). Primary behavioral outcome measures included the ADHD-rating scale, Youth Self Report, and Child Behavior Checklist all assessed pre- and post-intervention. **Results**: Behavioral problems decreased equally for both groups with medium to large effect sizes, range partial $\eta 2 = .08$ to .31, $p < .05$. Hence, the combination of NFB+TAU was not more effective than TAU-only on the behavioral outcome measures. In addition, reported adverse effects were similar for both groups. **Conclusions**: On behavioral outcome measures, the combination of neurofeedback and TAU was as effective as TAU-only for adolescents with ADHD symptoms. Considering the absence of additional behavioral effects in the current study, in combination with the limited knowledge of specific treatment effects, it is questionable whether theta/SMR neurofeedback for adolescents with ADHD and comorbid disorders in clinical practice should be used. Further research is warranted to investigate possible working mechanisms and (long-term) specific treatment effects of neurofeedback.

INTRODUCTION

Adolescents who show a persistent pattern of frequent inattention and/or hyperactivity-impulsivity symptoms - and for whom these symptoms are interfering with developmentally appropriate social, academic, or occupational functioning - are diagnosed with Attention Deficit/Hyperactivity Disorders (ADHD) (American Psychiatric Association, 2000). This is the most common neurodevelopment disorder with a prevalence of around 5,9% to 7,1% (Willcutt, 2012). Comorbid disorders like conduct disorders, mood and anxiety disorders are common (Barkley, 2006; Larson, Russ, Kahn, & Halfon, 2011). Additionally, in youngsters with autism spectrum disorders (ASD) estimations indicate high rates (ranging from 28% up to 78%) of ADHD comorbidity (Gjevik, Eldevik, Fjaeran-Granum, & Sponheim, 2011; Lee & Ousley, 2006; Simonoff et al., 2008).

Currently, best practice in ADHD treatment for adolescents consists of stimulant-medication, preferably in combination with behavior therapy (Wolraich et al., 2011). Stimulant-medication is effective in reducing ADHD symptoms (Faraone & Buitelaar, 2010) in 70% to 80% of the children suffering from ADHD (Greenhill et al., 2001), and in almost half of the children with ASD and comorbid ADHD (Research Units on Pediatric Psychopharmacology (RUPP) Autism Network, 2005). Thus, about a quarter of adolescents with ADHD and half of the adolescents with ASD and comorbid ADHD do not benefit (enough) from standard treatment with stimulant-medication. Moreover, mild adverse effects of stimulant-medication, such as decreased appetite, difficulty falling asleep and headaches are reported relatively often (Graham & Coghill, 2008; RUPP, 2005). Therefore, additional ADHD interventions that further increase effectiveness and reduce adverse effects to the standard ADHD treatment are warranted. In this respect, neurofeedback has been suggested as an intervention that is potentially effective in reducing ADHD symptoms by modifying brain activity in youngsters with ADHD (Gevensleben, Rothenberger, Moll, & Heinrich, 2012; Lofthouse, Arnold, Hersch, Hurt, & DeBeus, 2012; Moriyama et al., 2012) and ASD with comorbid ADHD (Holtmann et al., 2011).

Neurofeedback intends to alter brain activity by giving feedback of electroencephalogram (EEG) activity to patients. Notably, alterations in EEG activity patterns have been related to behavioral problems as seen in ADHD (Banaschewski & Brandeis, 2007; Snyder & Hall, 2006). Increased electroencephalogram (EEG) theta (4-7Hz) and decreased beta (13-30Hz) activity in ADHD-children compared to typically developing (TD) children, has been observed across studies (Snyder & Hall, 2006). Theta and beta activity can be related to vigilance and attention respectively (Banaschewski & Brandeis, 2007). Hence, adaptation of the theta- and beta-activity in children with ADHD, may lead to improved behavior. Likewise, sensorimotor rhythm (SMR)-activity (13-15Hz) measured above the central sulcus, is positively related to motor inhibition (Sterman & Wyrwicka, 1967; Sterman, Wyrwicka, & Roth, 1969). Correspondingly, it was reasoned by Lubar and Shouse (1976) that training aimed at increasing SMR-activity would improve inhibition in children with ADHD. As a result, the most frequently applied neurofeedback training protocols for ADHD aim to

decrease theta (4-7Hz) activity and increase SMR (12-15Hz) or beta (12-20Hz) activity, with electrode placement on the vertex (Cz) (Lofthouse et al., 2012; Loo & Makeig, 2012; Moriyama et al., 2012).

Based on previous reviews, claims on the effectiveness of neurofeedback for ADHD symptoms range from possibly effective (Gevensleben et al., 2012; Lofthouse et al., 2012; Moriyama et al., 2012) to 'efficacious and specific' (Arns, de Ridder, Strehl, Breteler, & Coenen, 2009). The estimated effect sizes varied between medium and large for the ADHD symptoms hyperactivity, impulsivity and attention (Arns et al., 2009). However, several methodological shortcomings have hampered many of the included studies: the majority of the studies were not randomized, sample sizes were small, and/or non-specific treatment effects were not controlled for. The more recently published reviews, using more rigorous inclusion criteria, report more conservative estimations of effects (Gevensleben et al., 2012; Lofthouse et al., 2012; Loo & Makeig, 2012; Moriyama et al., 2012) and results even dropped to non-significant levels when only studies were included with probably blinded assessments (Sonuga-Barke et al., 2013). In addition, a review pertaining to neurofeedback training in children with ASD concluded that neurofeedback was not effective for autism symptoms but possibly effective for comorbid ADHD symptoms (Holtmann et al., 2011). All in all, neurofeedback seems potentially effective though previous shortcomings in study design and unknown (negative) side effects preclude strong conclusions. To address these shortcomings, more controlled research is necessary to see which specific patients will profit from which specific neurofeedback training protocol (Gevensleben et al., 2012; Lofthouse et al., 2012). Furthermore, research is needed to see whether neurofeedback can be of additional value to multimodal treatment protocols (Gevensleben et al., 2012).

Therefore, the aim of the current study was to investigate the additional value of neurofeedback on behavior over treatment as usual (TAU) for adolescents diagnosed with ADHD and comorbid disorders, with a multicenter parallel randomized controlled trial design. It was expected that behavioral measures of attention would improve more in the group that received neurofeedback (in addition to TAU) than the group that received TAU-only. In addition, to address non-specific treatment effects and side effects of neurofeedback, indices of experienced improvement on non-standardized behavioral measures, headaches and sleep problems, as well as effects on autism symptoms were analyzed.

METHOD

Participants

Eligible participants were male adolescents with Dutch as their native language, between 12 and 24 years old, with a clinical DSM-IV-TR primary diagnosis of ADHD and a full-scale total intelligence quotient (TIQ)>80 on the Wechsler Intelligence Scale for Children (WISC-III) or the Wechsler Adult Intelligence Scale (WAIS-III) (Wechsler, 1991, 1997). Adolescents diagnosed with ASD (including: Autism, Asperger disorder and PDD-NOS) with notification of clinical ADHD symptoms equal to a full ADHD diagnosis were also included. ADHD symptoms were verified by a DSM-IV based Dutch semi-structured ADHD interview for adults (Kooij, 2002) and the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998; Sheehan et al., 1997). Exclusion criteria were neurological disorders, schizophrenia and other psychotic disorders.

Initially, a total of 90 adolescents were randomized over the interventions: combined neurofeedback and TAU (NFB+TAU; n=59) or TAU (n=31). The drop-out and exclusion rate did not differ for NFB+TAU, n=14 (23.7%) and TAU, n=5 (16.1%), p=.778 two-tailed Fisher exact test. At direct post-intervention analysis, NFB+TAU and TAU comprised n=45 and n=26 adolescents, respectively. Drop-out reasons included motivational and/or organizational reasons NFB+TAU=9; TAU=5) and transfer to another region (NFB+TAU=2). Three adolescents were excluded from analyses because of occurrence of psychotic symptoms (NFB+TAU=2) and borderline disorder (NFB+TAU=1) and hence these data were considered not reliable. A participant flow diagram is presented in Figure 1.

Medication use and presence of comorbid disorders were allowed. Comorbid disorders included: Depressive disorders (4), Anxiety disorders (2), Substance related disorders (4), Conduct disorders (4), Learning disorders (6), Communication disorders (1), Tic disorders (1) Elimination Disorders (1), Adjustment disorders (1), Reactive attachment disorder (1). The final group characteristics are listed in Table 1.

Trial Design

This was a multicenter parallel-group study, stratified for age (12 through 16, 16 through 20, 20 through 24 years of age) and with imbalanced randomization [2:1] for NFB+TAU versus TAU-only. Randomization was generated using an online automatic random number generator (Dallal, 2007). The block lengths were 3, 6, 9, and 12 and varied randomly. An independent administrative employee was responsible for the assignment of participants to their groups. The investigators were blind for block-lengths and for the number of participants in each stratification group. After pre-intervention assessments the investigator e-mailed the administrative employee to apply randomization. The same day, the participant (and if applicable, his parents) was notified whether he would receive neurofeedback intervention or not. Participants, parents, neurofeedback trainers and clinical professionals were aware of the allocated arm randomization. The outcome assessor and

neurofeedback trainer were not the same person. All data entry was performed blind to the allocated arm and was checked twice by different research interns or assistants.

Previous estimated effect sizes for decreased ADHD symptoms by neurofeedback range from medium to large. Sample size estimation was done by G*power version 3.1.5.1 (Faul, Erdefelder, Lang, & Buchner, 2007). For an ANOVA repeated measures, within-between interaction a total sample size of 46 (or 23 per intervention arm) was calculated to be sufficient to detect a medium effect size (f=.25) with an alpha .05 and a power of 90%.

This trial is registered in the Dutch trial register (Ref. no: added in non-blinded manuscript) and is funded by: (Government grant added in non-blinded manuscript). In this article, the CONSORT 2010 guidelines for reporting parallel group randomized trials were followed (Schulz, Altman, & Moher, 2010).

Interventions

Treatment as usual (TAU). In the TAU-group, the participants received treatment as prescribed by the main therapist of the participating center for child and adolescent psychiatry (GGzE, GGz Breburg, Reinier van Arkel group). TAU was monitored through an intervention questionnaire based on the 'Dutch national basic program ADHD for children and adolescents' (Vink & Van Wamel, 2007). Behavioral interventions included cognitive behavioral therapy, systemic therapy, and/or supportive counseling, either directed at the adolescent and/or at the parent(s). Stimulant medication use included immediate release methylphenidate, sustained release methylphenidate and dexamphetamine. Atomoxetine was used by two participants at study entry. Because of the suggested similar clinical effects of stimulant medication and atomoxetine, in the analyses these two participants were categorized within the group of stimulant-medicated adolescents. Adherence to prescribed medication was verified by questioning the participants whether they took the prescribed medication. Stimulant medication use and received behavioral therapy did not differ between the group receiving TAU-only and the group who received neurofeedback in addition to TAU (see Table 1).

Neurofeedback in addition to TAU. Neurofeedback training was carried out over a period of around five months (25 weeks), with two to three training sessions every week. Each participant was offered 40 training sessions of 30 minutes in total. The mean number who followed the training sessions was 37 (36.98± 4.94) with a minimum of 19 sessions. A neuropsychologist, EEG Biofeedback EEG Spectrum International Inc. certified, accredited by the Biofeedback Certification International Alliance (BCIA) (MB), trained the psychologists who gave the neurofeedback training. The treatment protocol was based on rationales of J. F. Lubar (2003), J. O. Lubar and Lubar (1984), and Fuchs, Birbaumer, Lutzenberger, Gruzelier, and Kaiser (2003). The aim of the treatment was to increase SMR-activity, while simultaneously decreasing theta, alpha and electromyographic (EMG) activity due to muscle tension to ensure an attentive and relaxed state of engagement with an altered EEG state for

longer periods of time (J. F. Lubar, 2003). The treatment protocol therefore consisted of decreasing low frequency bands (4-11Hz), increasing SMR-activity (12-15Hz) and decreasing high beta/gamma (22-36Hz) at Cz. Inhibition of higher beta/gamma frequency band was conducted in this study to minimize the increase of SMR-activity by increased muscle-tension, and to decrease potential high beta that seems to occur in an estimated 10-20% of children with ADHD (Snyder & Hall, 2006).

Training was conducted on Cz, referred to linked mastoids. The EEG-signal was transmitted to the computer by the Brainquiry PET EEG 2 channel bipolar system (Braininquiry): a DC amplifier with active electrodes, a low-pass anti-aliasing filter of 40 Hz, a sample rate of 200 Hz and a 29 bit AD resolution. Neurofeedback training was conducted with 'EEGer' neurofeedback software version 4.2.1 (EEGer Spectrum Systems). The EEG-signal was accordingly band pass-filtered in the different frequency bands with an exponentially weighted moving average filter over 0.5 second to produce a short-term average. Each frequency band involved a 0.25Hz increment step size reward filter. Each training session was divided into ten 3-minute epochs. Artifact rejection thresholds for the raw EEG-signal were set to 60μV, to prevent the effect of gross movements from the participants. Relative thresholds for each frequency band were set to accept the signal 80%and to reject the signal 20% of the time. Thresholds were calculated to correspond to the mean amplitude in μV of each frequency band over the last 30 seconds of input and were calculated after 30 seconds from the beginning of each 3-minute session. For the first 30 seconds, thresholds of former 3-minute session were preserved.

The signal was visually presented to the participant on a screen by simple graphics, which represented the different frequency bands by three colored boxes. The colors of the boxes were moving: sometimes a color did not totally fill the box and sometimes the color exceeded the borders of the box. The participant was instructed that the left, purple-colored box represented slow wave activity (4-11Hz) and the right, yellow-colored box represented fast wave activity and muscle tension (22-36Hz). For both these boxes the colors were to be kept in the drawn box (inhibit). The middle, blue-colored box represented the 'good' waves (SMR 12-15Hz) and the participant was instructed that this color should exceed the borders of the box and get as wide as possible (reward). At the moment the signal for all frequency bands fulfilled all threshold criteria, audible feedback was given by a short .25-second beep. Subsequently, the participants obtained a point that increased the score on the bottom of the screen.

Outcome Measures

Primary outcome measures included three behavioral questionnaires. Secondary outcome measures consisted of non-standardized behavioral measures, side effects on reported sleeping problems and headaches, and autism symptoms. Neuropsychological and electro-physiological outcome measures assessed during the study will be reported elsewhere.

Primary behavioral outcome measures. The ADHD-rating scale is a DSM-IV-based self-report for adults (Kooij et al., 2008; Kooij et al., 2005). This is an adapted form of DuPaul et al. (1998)

which contains 23 items rated on a 4-point scale ranging from 'rarely or never' to 'very often'. Items were filled out for occurrence of current symptoms (in the past 6 months) at pre- and post-intervention. Two nine-item subscales were used: inattention and hyperactivity/ impulsivity (Kooij et al., 2008; Kooij et al., 2005).

The Child Behavior Checklist (CBCL) and the Youth Self Report (YSR) (Achenbach, 1991) are questionnaires that cover respectively parent-reported and self-reported behavioral and emotional problems for children and adolescents up to 18 years old. In this study, the subscale attention problems, the broadband scale externalizing problems and the global scale total problems were used. For participants over 18 years also the CBCL and YSR were used, since most of them were still attending school and living with their parents.

Secondary outcome measures. Behavioral changes on non-standardized measures, autism symptoms and side effects were included as secondary outcome measures. Experienced behavioral changes on non-standardized measures at post-intervention ('Did you notice any behavioral changes during the last period (6-months)?') were scored as no improvement (0) or improvement (1) for overall behavior, attention, and hyperactivity/impulsivity.

Autism symptoms were screened with the Autism-Spectrum Quotient (AQ)-adolescent version for individuals with normal intelligence (Baron-Cohen, Hoekstra, Knickmeyer, & Wheelwright, 2006). Parents or other relevant adults filled out the AQ-adolescent. AQ-questionnaires were excluded from analyses when three or more answers were missing.

Headache frequency ('Did you experience headaches during the last 6-months and what was the frequency of the headaches?') were scored as never (0), sometimes (1), 1-2/month (2), 3-8/month (3) and >3/week (4). Sleep pattern ('Do you have difficulties with: (I) falling asleep / (II) sleeping through / (III) getting up in the morning? and (IV) are you feeling sleepy during the day?'), was scored dichotomously per question (I-IV) as not problematic (0) and problematic (1) and summarized.

Procedure

Prior to the start of the study, approval was obtained from the medical ethics committee for mental health institutions in the Netherlands (Ref.no: NL 24776.097.08 CCMO). The study took place in three centers for child and adolescent psychiatry (GGzE, GGz Breburg, Reinier van Arkel group) in the South of the Netherlands. After the study was explained (verbally and in writing), written informed consent was obtained from each participant. For those younger than 18, parents also provided written informed consent.

At pre-intervention, participants were seen on three occasions for the administration of behavioral questionnaires, neuropsychological tests, an assessment of intellectual functioning using the WAIS- or WISC-intelligence test and EEG measurements. In cases where participants were on medication, medication intake was also continued on the day of assessment.

Interventions took place between December 2009 and July 2012. The duration of the intervention period was approximately five months (25 weeks).

At post-intervention assessment, behavioral questionnaires and neuropsychological tests were assessed for all 71 participants. One participant refused to complete the YSR. For two participants, reported headache frequency was missing.

Parents or relevant adults received the parent-report questionnaires (CBCL and AQ-adolescent) by mail, requesting their return pre- and post-intervention. CBCL-data were incomplete or missing for 13 participants. The AQ-questionnaire was missing or incomplete for 19 participants.

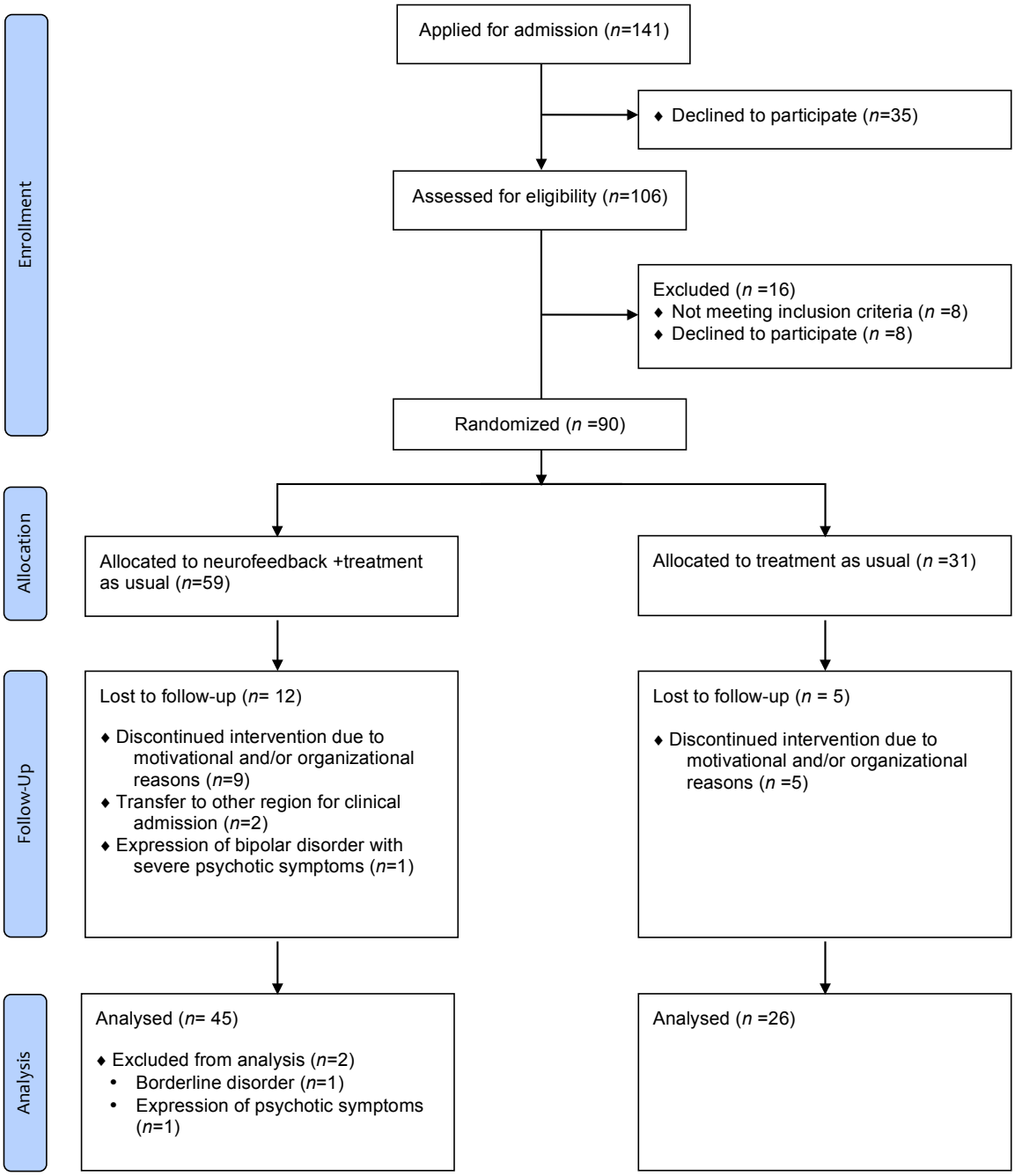
Statistical Analysis

All analyses were performed using SPSS version 19.0. Effects were considered significant if $p<.05$. Differences on group characteristics were analyzed with a one-way ANOVA or a chi-square test (χ^2) with Fisher exact correction. Attrition analyses, for behavioral data with smaller sample size than the total sample size due to missing or incomplete data, were performed by comparing the analyzed subsample for a particular measure to the total sample on group characteristics and other pre-intervention primary behavioral outcome measures with a one-way ANOVA.

A completion analysis was applied involving the participants who finished all assessments up to post-intervention (including neurofeedback training, if applicable), in order to determine whether neurofeedback had additional value after completion of the training. The effect of neurofeedback training was investigated using a Generalized Linear Model (GLM) with between- and within-subjects factors. The analysis was applied for all the primary behavioral outcome measures separately with intervention group as between-subject factors and time [e.g. between pre-intervention (t1) and post-intervention (t2)] as within-subjects factor. The full factorial models were tested. All behavioral effects were evaluated using multivariate test criteria. Effect sizes are expressed in percentage of explained variance in partial η2 (η_p^2). In addition, the adjusted difference at post-intervention (AD_{t2-t1}) and 95% confidence interval [95% CI] were noted. Post hoc analyses were performed with the addition of stimulant medication use at pre-intervention and diagnostic group (ADHD or ASD with comorbid ADHD) as between-subject factor to the GLM. To control for potential outcome bias of the drop-outs (n=16) after randomization post-hoc analyses were performed based on imputation with Last Observation Carried Forward (LOCF) for the total group as randomized with the exception of the three excluded participants.

Non-standardized secondary behavioral measures were examined by calculation of the relative risk (RR). Change is considered significant when the RR and 95% CI do not include [1.0]. Frequency of headaches, total sleeping problems and autism symptoms were analyzed using a GLM with between- and within-subjects factors as described in the primary outcome measures.

Figure 1: *Participant Flow Diagram*



RESULTS

Group Characteristics

There were no baseline differences for group characteristics between the NFB+TAU group and the TAU-group (Table 1). In both groups, most participants who used stimulant medication started taking stimulant medication more than 6 months before pre-intervention. The mean (standard deviation) doses of stimulant medication in mg was 37.19 (16.41), 95% CI= [31.64, 42.75], range [10, 72] and did not differ between the groups, $F(1, 34)=.21$, $p=.65$ $\eta_p^2=.01$. The TAU-group seemed to have a somewhat higher total intelligence quotient (TIQ) than the NFB+TAU group. Performance intelligence quotient (PIQ) was similar for both groups. There were no group differences at pre-intervention assessment for behavioral primary outcome measures.

Table 1: Group characteristics[1]

	TOTAL	NFB+TAU	TAU	GROUP	
	N=71	*n*=45	*n*=26	F	*p*
Age in Years	16.14(3.32)	16.09(3.33)	16.2(3.37)	.03	.86
Primary DSM diagnoses					
ADHD	47(66%)	29(64%)	18(69%)		.79
ASD+ADHD	24(34%)	16(36%)	8(31%)		.79
GAF-scores	54.66(6.74)	53.80(7.07)	56.15(5.95)	2.04	.16
Stimulant Medication t1	36(51%)	20(44%)	16(62%)		.22
Months of intake before t1				3.74	.46
Up to 3 months	6 (8%)	4(9%)	2(8%)		
3 to 6 months	3(4%)	2(4%)	1(4%)		
6 to 12 months	4(6%)	3(7%)	1(4%)		
12 months or more	23(32%)	11(24%)	12(46%)		
Stimulant-free	35(49%)	25(56%)	10(39%)		
Started after t1	6(8%)	3(7%)	3(12%)		.66
Stopped after t1	9(13%)	5(11%)	4(15%)		.72
Behavioral interventions[2]					
Adolescent	26(37%)	14(31%)	12(46%)		.32
Parent	20(28%)	12(27%)	8(30%)		.79
MINI ADHD Inattention	5.63(2.61)	5.38(2,56)	6.08(2.68)	1.18	.28
MINI ADHD H/I	4.00(2.46)	4.16(2.58)	3.73(2.29)	.49	.49
ADHD-rating Childhood Inattention[3]	6.07(2.66)	5.67(2.92)	6.77(2.01)	2.90	.09
ADHD-rating Childhood H/I[3]	4.94(2.87)	4.58(2.99)	5.58(2.60)	2.02	.16
IQ Discrepancy profile[4]	24(34%)	14(31%)	10(38%)		.61
Total IQ	100.66(11.30)	98.62 (10.38)	104.19 (12.15)	4.18	.05
VIQ	102.37(12.89)	100.16(11.43)	106.19(14.54)	3.76	.06
PIQ	99.51(11.93)	98.44(11.20)	101.35(13.12)	.97	.33

Note: t1 is pre-intervention; 1Data are means (SD) or numbers (%); 2Behavrioural interventions followed between pre- and post-intervention (t1-t2). 3ADHD-rating scale retrospective self-reported childhood symptoms for Inattention and Hyperactivity/Impulsivity (HI). Group characteristics did not differ between groups. 4Intelligence Quotient (IQ) Discrepancy profile is considered as a profile with a difference score between verbal IQ (VIQ) and performance IQ (PIQ) of 15 points or more. Because of the discrepancy profiles VIQ and PIQ are noted separately.

Attrition Analysis

Attrition analysis showed that the drop-out group (N=16) did not differ from the completers (N=71) on group characteristics or primary behavioral outcome measures. Attrition analyses for the subsamples with respect to the YSR (N=70), CBCL (N=58), reported headaches frequency (N=69) or AQ-adolescent (N=52) showed no difference from the completers (N=71) on group characteristics or primary behavioral outcome measures at pre-intervention.

Behavioral Measures

Behavioral primary outcome measures are summarized in Table 2. The ADHD-rating scale showed that both inattention and hyperactivity/impulsivity (HI) decreased over time, for the NFB+TAU group and TAU-group alike. The YSR and the CBCL revealed the same pattern for attention, externalizing and total problems, again, irrespective of the groups.

Stimulant medication use and diagnostic group

Post hoc analysis for stimulant medication use or diagnostic group showed no difference between stimulant medicated and stimulant-free adolescents or diagnosis on the behavioral primary outcome measures.

LOCF

Post hoc analysis, to control for potential outcome bias due to drop-out, showed similar outcomes on all measures with a decrease of behavioral problems over time for all adolescents (*N*=87), irrespective of treatment group (NFB+TAU or TAU).

Table 2: Behavioral primary outcome measures

	Pre-Intervention		Post-Intervention		Adjusted difference [95% CI] at post intervention (t2-t1)	Time (t1 to t2) [3]		NFB+TAU and TAU over time		Post Hoc Med. Use over time [4]		Post Hoc ASD+ and ADHD over time[5]		Post Hoc Time based on LOCF[6]	
	NFB+TAU	TAU	NFB+TAU	TAU											
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)		F	η_p^2	F	η_p^2	F	η_p^2	F	η_p^2	F	η_p^2
ADHD-rating[1]	*n*=45	*n* =26	*n* =45	*n* =26											
Inattention	4.40(2.49)	5.27(2.16)	2.84(2.59)	3.62(2.45)	-1.61[-2.17, -1.04]	31.57 ***	.31	.03	.00	1.13	.02	.91	.01	30.08***	.26
H/I	3.44(2.12)	3.27(2.01)	2.36(2.16)	2.38(2.14)	-0.99[-1.53, -.44]	13.01 ***	.16	.14	.00	1.20	.02	1.10	.02	12.52***	.13
YSR[2]	*n* =44	*n* =26	*n* =44	*n* =26											
Attention	9.45(3.29)	9.92(3.24)	7.45(3.45)	9.27(3.55)	-1.33[-2.13, -.53]	11.00 **	.14	2.83	.04	.01	.00	.34	.01	10.14**	.11
Extern.	15.95(10.02)	14.92(7.38)	13.77(7.42)	12.73(7.60)	-2.19[-3.69, -.68]	8.42 **	.11	.00	.00	.48	.01	.79	.01	8.26**	.09
Total	48.50(22.01)	52.58(18.89)	40.43(18.24)	46.12(20.17)	-7.27[-11.39, -3.14]	12.35 ***	.15	.15	.00	.07	.00	3.15†	.05	11.85***	.12
CBCL	*n* =37	*n* =21	*n* =37	*n* =21											
Attention	11.16(3.64)	12.33(2.67)	9.67(3.24)	10.48(3.53)	-1.63[-2.41, -.85]	17.46 ***	.24	.34	.00	.05	.00	.47	.01	16.18***	.18
Extern.	18.05(11.46)	18.95(12.35)	16.41(12.75)	15.95(13.72)	-2.32[-4.50, -.15]	4.59 *	.08	.39	.01	.03	.00	1.25	.02	4.48*	.06
Total	60.81(28.57)	63.77(27.00)	53.35(27.55)	52.81(30.28)	-9.16[-14.44, -3.88]	12.08 ***	.18	.42	.01	.30	.01	1.44	.03	11.45**	.13

Note: †=p<.10,*=p<.05, **=p<.01, ***=p<.001, 1ADHD-rating scale self-reported current symptoms for Inattention and Hyperactive/Impulsive (H/I), 2YSR and CBCL scales: Attention problems, Externalizing (Extern.) problems and Total problems 3GLM ANOVA with time (t1 to t2) as within factor and NFB+TAU and TAU as between factor ADHD-rating scale *df*(1,69); YSR *df* (1,68); CBCL *df* (1,56), 4Post hoc analysis for stimulant medication use; ADHD-rating scale *df* (1,67); YSR *df* (1,66); CBCL *df* (1,54). 5Post hoc analysis for diagnostic group ADHD versus ASD with comorbid ADHD; ADHD-rating scale *df* (1,67); YSR *df* (1,66); CBCL *df* (1,54). There were no interactions between time, intervention group and stimulant medication use or time, intervention group and diagnostic group (ADHD or ASD+ADHD); 6Post hoc analysis as randomized based on LOCF, ADHD-rating scale *df* (1,85); YSR *df* (1,85); CBCL *df* (1,76). There were no interactions between time and intervention group.

Secondary Outcome Measures

A larger percentage of NFB+TAU participants reported improvement in attention, compared to TAU on the non-standardized behavioral question. Overall improvement was reported by 29 of the 45 (64%) in the NFB+TAU group and by 10 of the 26 (38%) in the TAU-group, RR=1.68, 95%CI=[0.98, 2.85]. More specifically, improvement in attention was reported by 17 (38%) of the NFB+TAU group and in 3 (12%) of the TAU-group. Participants in the NFB+TAU group were 3.27 times more likely to report attention improvement than the TAU-group, RR=3.27, 95%CI=[1.06, 10.12]. Improvement in hyperactivity/impulsivity did not differ between the groups and was reported in the NFB+TAU group by 16 (36%) participants and by 6 (23%) in the TAU-group, RR=.84; 95%CI=[0.62, 1.13].

Parent-reported autism symptoms showed no decline over time (Table 3). No differences in autism symptoms between the NFB+TAU group and TAU-group were found or interactions for time and group.

There were no changes over time or interactions between time and group for headache frequency and sleeping problems. The frequency of headaches and amount of reported sleeping problems stayed the same over time for both groups (Table 3). There was however an interaction for stimulant medication use over time with post-hoc analyses showing that stimulant-free adolescents report fewer headaches over time (n=33, pre-intervention (t1) M=1.67, SD=1,05, post-intervention (t2) M=1.06, SD=1.27, $AD_{t2\text{-}t1}$=-.61, 95%CI=[-0.99, -0.22], η_p^2 =.24, whereas for stimulant-medicated adolescents the amount of headaches stayed the same over time (n=36, pre-intervention (t1) M=1.58 SD=.97, post-intervention (t2) M=1.83, SD=1.28, $AD_{t2\text{-}t1}$ =.25, 95%CI=[-0.17, 0.67]), F(1,65)=5.45, p=.023, η_p^2=.08.

Table 3: Secondary outcome measures: autism symptoms and side effects

	Pre-Intervention		Post-Intervention		Adjusted	ANOVA		ANOVA		Post Hoc		Post Hoc		Post Hoc	
	NFB+TAU	TAU	NFB+TAU	TAU	difference [95% CI] at post intervention (t2-t1)	TIME (t1 to t2)[1]		NFB+TAU and TAU over time[1]		Med. Use over time[2]		ASD+ and ADHD over time[3]		Time based on LOCF[4]	
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)		F	η_p^2	F	η_p^2	F	η_p^2	F	η_p^2	F	η_p^2
AQ-Adolescent version	*n* =32	*n* =20	*n* =32	*n* =20											
Parent Report	26.27(8.09)	23.40(5.24)	25.19(8.16)	22.90(6.78)	-.79[-2.30, .72]	1.10	.02	.15	.00	.02	.00	.81	.02	1.07	.01
Headaches	*n* =45	*n* =24	*n* =45	*n* =24											
Scale 0 to 4	1.56(0.97)	1.75(1.07)	1.33(1.37)	1.71(1.23)	-.13[-.44, .18]	.71	.01	.33	.00	5.45*	.08	1.22	.02	.72	.01
Sleep Problems	*n* =45	*n* =26	*n* =45	*n* =26											
Scale 0 to 4	1.44(1.03)	1.73(1.04)	1.62(1.05)	1.46(.99)	-.05[-.33, .24]	.10	.00	2.43	.03	.45	.01	.00	.00	.12	.03

Note: *=p<.05; 1GLM ANOVA with time (t1 to t2) as within factor and NFB+TAU and TAU as between factor; AQ-Adolescent *df* (1,50); Headaches *df* (1,67); Sleep problems df(1,69), 2Post hoc analysis for stimulant medication use; AQ-Adolescent *df*(1,48); Headaches *df* (1,65); Sleep problems *df* (1,67). 3Post hoc analysis for diagnostic group ADHD versus ASD with comorbid ADHD; AQ-Adolescent *df* (1,48); Headaches *df* (1,65); Sleep problems *df* (1,67). There were no interactions between time, intervention group and stimulant medication use or time, intervention group and diagnostic group (ADHD or ASD+ADHD). 4 Post hoc analyses as randomized based on LOCF, AQ-Adolescent *df* (1,73); Headaches *df* (1,80); Sleep problems *df* (1,)). There were no interactions between time and intervention group.

DISCUSSION

The present study examined the additional value of neurofeedback on behavior over TAU with a multicenter parallel-randomized controlled trial design. A decline in behavioral problems of ADHD in adolescents in both treatment groups was found. Hence, an additional effect of neurofeedback over TAU on the primary behavioral outcome measures was not observed. However, when asked for changes, adolescents who received neurofeedback in addition to TAU more often reported improvement in attention than adolescents who received only TAU.

As for the large decrease in behavioral problems of ADHD between pre- and post-intervention assessment on behavioral outcome measures, a recently published randomized controlled trial showed similar behavioral improvements in children with ADHD receiving neurofeedback alone, stimulant medication, or combined stimulant medication and neurofeedback (Duric, Assmus, Gundersen, & Elgen, 2012). In line with the results in the present, improvement was observed regardless of type of treatment. In addition, double blinded RCT's also were not able to show superiority for neurofeedback over sham-neurofeedback to improve behavior (Arnold et al., 2013; Perreau-Linck, Lessard, Levesque, & Beauregard, 2010; van Dongen-Boomsma, Vollebregt, Slaats-Willemse, & Buitelaar, 2013) or neurocognitive functioning (Vollebregt, van Dongen-Boomsma, Buitelaar, & Slaats-Willemse, 2013) in children with ADHD. The results of the current RCT are in line with the neurocognitive outcomes (Bink et al., In Press). In contrast, a previous large non-randomized study found additional effects on behavior with more improvement in attention for children who received neurofeedback in addition to a combined intervention of medication and behavioral therapy than children who received only medication and behavioral therapy one year post-intervention (Monastra, Monastra, & George, 2002). Possibly, the non-randomized nature of this study may have caused selection biases such as differences between parents with a preference for neurofeedback and parents who choose conventional treatment that may account for this discrepancy. Parents with a preference for neurofeedback might be more inclined to motivate their child to change and thereby make an environment that enables the child to improve more on behavioral attention measures.

In this study, improvement in attention was reported more often by adolescents who received neurofeedback in addition to TAU than adolescents who received TAU-only. This is remarkable when compared to the outcome on the other standardized self- and parent-reported questionnaires, which show similar behavioral improvements over time for both groups. It might be that the adolescents in the NFB+TAU group were more aware of the improvement, or more prone to point out the improvement, because of the investment they put in the neurofeedback intervention.

Results show that autism symptoms were not influenced by treatment (NFB+TAU or TAU). Parents did not report significant changes in autism symptoms over time. This is in line with a recent review, which concluded that neurofeedback treatment does not seem to improve core autistic symptoms (Holtmann et al., 2011). On the other behavioral measures used in the current study, it

seems that behavioral problems diminished over time for the adolescents with ADHD as well as for the adolescents with ASD and comorbid ADHD.

Side effects as a result of neurofeedback were not found: no differences in negative adverse effects with respect to sleep pattern or headaches were found between the intervention groups. This is in accordance with two double-blinded studies that showed no adverse effects for neurofeedback or placebo-neurofeedback training (Arnold et al., 2013; van Dongen-Boomsma et al., 2013). The other randomized trials did not address adverse effects. Positive effects of SMR-neurofeedback in relation to quality of sleep, have been hypothesized (Arns & Kenemans, 2012). Sleep spindle activity is activity in the SMR frequency-band (12-15Hz). Neurofeedback aimed at an increase of SMR-activity has been positively related to the increase of sleep spindle density during sleep and thereby the quality of sleep (Arns & Kenemans, 2012). However, the present study did not find improvements in sleep patterns. There was a decrease in the frequency of headaches over time for stimulant-free adolescents. Headache is a common adverse effect of stimulant medication use (Graham & Coghill, 2008), as a result, this might be the reason that stimulant-medicated adolescents did not experience a reduction in headache frequency over time.

The present study is the first to investigate effects of neurofeedback as an additional treatment to TAU in a naturalistic multimodal treatment setting applying a randomized controlled trial design. The implementation of neurofeedback in addition to TAU increases the ecological validity of the study. Although there was no selective dropout, this design also includes several limitations. For example, the target population consists of a heterogeneous group of male adolescents with complex problems. It might be that neurofeedback is only effective for a specific part of the population with ADHD symptoms. Furthermore, it could be that the used theta/SMR-training is not the optimal neurofeedback protocol for ADHD. Loo and Makeig (2012) have already stated that, based on the current literature, theta/beta training results are not indicative to applying this training as an additional treatment to standard practice. Other neurofeedback protocols, like the training of slow cortical potentials (SCP <0.1Hz) or training of other frequency bands, might lead to better results. Another limitation is the intensity of the training: adolescents who received neurofeedback were trained approximately twice a week over a total period of 5 months. Perhaps a shorter and more intensive training period, with three or more training sessions a week, is needed for inducing clinical relevant behavioral changes. Another limitation is the use of self- and parent reported behavioral measures in combination with the non-blinded nature of the study. Because of the investment of parents and participants in the neurofeedback intervention, this might have increased the risk of a bias. It could be expected that the outcomes for the NFB+TAU condition were positively biased compared to TAU. A recent meta-analysis (Sonuga-Barke et al., 2013) pointed out that the neurofeedback treatment showed significant effects when non-blinded assessments were considered, but not when only probably blinded assessments were considered. In the current study, however, results showed no additional effects of neurofeedback on behavioral measures and as a consequence the effects were not likely influenced by such a positive bias. In addition, ceiling effects in improvement on the behavioral

measures by the TAU or as a result of developmental related improvement and multiple testing could be the cause for not finding additional effects for neurofeedback. Given the sample size of the study, effects of neurofeedback should be medium to large to be reliably detected; as a result small effects might be missed. Nevertheless, neurofeedback is a costly intervention in time investment for patients, parents, therapists, and health care resources. The important question therefore is what effect size would make neurofeedback cost-effective and clinically relevant.

In conclusion, the present study showed that on behavioral outcome measures, the combination of neurofeedback and TAU was as effective as TAU-only for adolescents with ADHD symptoms. Neurofeedback in combination with TAU and TAU-only both showed significantly improved behavior, mainly in attention, at post-intervention. Considering the absence of additional behavioral effects in the current study, in combination with the limited knowledge of specific treatment effects of neurofeedback, it is questionable whether theta/SMR neurofeedback for adolescents with ADHD and comorbid disorders should be used in clinical practice. Further research is warranted to investigate possible working mechanisms and (long-term) specific treatment effects of neurofeedback.

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CHAPTER 6

Neurocognitive Effects of Neurofeedback in Adolescents with ADHD: An RCT

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ABSTRACT

Objective: Neurofeedback aims to reduce Attention Deficit/Hyperactivity Disorder (ADHD) symptoms, mainly attention problems. However, the additional influence of neurofeedback over treatment as usual (TAU) on neurocognitive functioning for adolescents with ADHD remains unclear. *Method*: Using a multicenter parallel-randomized controlled trial (RCT) design, male adolescents with a DSM-IV-TR diagnosis ADHD (mean age 16.1, range 12-24) were randomized to receive either a combination of TAU and neurofeedback (NFB+TAU, *n*=45) or TAU (*n*=26). Randomization was computer-generated and stratified for age group (ages 12 through 15, 16 through 20, and 21 through 24 years). The neurofeedback intervention consisted of approximately 37 sessions over a period of 25 weeks of theta/sensorimotor rhythm (SMR) training on the vertex (Cz). Primary neurocognitive outcomes included performance parameters derived from the D2 test of attention, the digit span backwards, the Stroop color-word test and the Tower of London, all assessed pre- and post-intervention. Data were collected between December 2009 and July 2012. *Results*: At post-intervention, outcomes of attention and/or motor speed were improved with faster processing times for both intervention conditions with medium to large effect sizes (range η_p^2= .08-.54, *p* values <.023). In both groups, no improvements for higher executive functions were observed. Results might partly resemble practice effects. *Conclusion*: Although neurocognitive outcomes improved in all adolescents receiving treatment for ADHD, no additional value for neurofeedback over TAU was observed. Hence, this study does not provide evidence for using theta/SMR neurofeedback to enhance neurocognitive performance as additional intervention to TAU for adolescents with ADHD symptoms.

INTRODUCTION

Attention Deficit/Hyperactivity Disorder (ADHD) is the most common neurodevelopmental disorder with a worldwide prevalence of around 5% (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007; Willcutt, 2012). In addition, estimations of ADHD comorbidity in autism spectrum disorders (ASD) range between 30% and 78% (Gjevik, Eldevik, Fjaeran-Granum, & Sponheim, 2011; Holtmann, Bolte, & Poustka, 2007; Lee & Ousley, 2006; Simonoff et al., 2008). Best practice for reducing ADHD symptoms consists of stimulant-medication, and/or behavioral therapy. Stimulant-medication is effective in reducing ADHD symptoms in youngsters with ADHD (Faraone & Buitelaar, 2010; Greenhill et al., 2001) and effective, although possible to a lesser extend, for treatment of ADHD in youngsters with combined ASD and ADHD (Cortese, Castelnau, Morcillo, Roux, & Bonnet-Brilhault, 2012; RUPP, 2005). Similarly, neurocognitive dysfunction as associated in ADHD, generally seems to improve with the use of stimulant medication (Coghill et al.). A recent review indicates that generally remittance of ADHD symptoms is not associated with improved neurocognitive functions: adolescents with remitted ADHD still experience decreased neurocognitive performance (van Lieshout, Luman, Buitelaar, Rommelse, & Oosterlaan, 2013). This indicates that ADHD-symptomatology and neurocognitive functioning should be considered as separate treatment outcome measures (Coghill et al.). Moreover, although stimulant-medication seems effective in reducing ADHD symptoms (Cortese et al., 2012; Faraone & Buitelaar, 2010; Greenhill et al., 2001; RUPP, 2005) and improving neurocognitive functioning (Coghill et al.), the majority of adolescents above the age of 15 discontinue stimulant-medication use despite the persistent course of the disorder (Zetterqvist, Asherson, Halldner, Langstrom, & Larsson, 2012). Therefore, additional interventions to the current treatment as usual (TAU) to further reduce ADHD symptoms enduringly and simultaneously improve neurocognitive functioning are warranted. In this respect, neurofeedback, which is seen as a potential effective intervention for reducing ADHD symptoms in ADHD(Lofthouse, Arnold, Hersch, Hurt, & DeBeus, 2012; Moriyama et al., 2012) and ASD,(Holtmann et al., 2011) might as well be able to improve neurocognitive functioning.

Neurofeedback is based on the principle of operant conditioning and aims to alter brain functioning by giving real-time feedback of electroencephalogram (EEG) activity to the patient. Children with ADHD show an increased theta activity and decreased beta activity compared with typically developing children (Snyder & Hall, 2006). Accordingly, the most frequently used neurofeedback protocol is the theta/beta training, which aims to decrease theta (4-7Hz) and increase SMR (12-15Hz) or beta (12-20Hz) (Lofthouse et al., 2012; Loo & Makeig, 2012; Moriyama et al., 2012). Following theta/beta training, one study found changes in brain functioning as reflected in a decrease of posterior-midline theta activity (Gevensleben, Holl, Albrecht, Schlamp, et al., 2009). In addition, the decrease in theta activity was related to the decrease in ADHD symptoms as reported by parents (Gevensleben, Holl, Albrecht, Schlamp, et al., 2009). Two other studies showed similar improvement in attention on behavioral questionnaires over time for children with ADHD who were treated with neurofeedback and/or with stimulant medication (Duric, Assmus, Gundersen, & Elgen,

2012; Meisel, Servera, Garcia-Banda, Cardo, & Moreno, 2013). Thus, some randomized controlled trials (RCT) (Duric et al., 2012; Gevensleben, Holl, Albrecht, Schlamp, et al., 2009; Meisel et al., 2013) have shown improvements in ADHD symptomatology, as reported by parents. However, these studies (Duric et al., 2012; Gevensleben, Holl, Albrecht, Schlamp, et al., 2009; Meisel et al., 2013) did not report on intervention effects in relation to neurocognitive functioning.

To date, the findings of four blinded RCT studies (Arnold et al., 2012; Bakhshayesh, Hansch, Wyschkon, Rezai, & Esser, 2011; Logemann, Lansbergen, Van Os, Bocker, & Kenemans, 2010; Vollebregt, van Dongen-Boomsma, Buitelaar, & Slaats-Willemse, 2013) on neurofeedback for ADHD in which neurocognitive measures were reported, are inconsistent. In one single-blinded study, children with ADHD who received neurofeedback improved more in reaction time (RT) and accuracy than those receiving electromyography (EMG) biofeedback (Bakhshayesh et al., 2011). In contrast, three double-blind studies failed to find additional improvement on neurocognitive measures for neurofeedback over sham-neurofeedback in children with ADHD (Arnold et al., 2012; Vollebregt et al., 2013) and healthy students with ADHD features (Logemann et al., 2010). These neurocognitive outcomes (Arnold et al., 2012; Logemann et al., 2010; Vollebregt et al., 2013) are in line with the behavioral outcomes of blinded studies that fail to find additional value of neurofeedback over sham-neurofeedback (Arnold et al., 2012; Logemann et al., 2010; Sonuga-Barke et al., 2013; van Dongen-Boomsma, Vollebregt, Slaats-Willemse, & Buitelaar, 2013).

To summarize, although neurofeedback is seen as a potentially effective intervention for reduction of ADHD symptoms in children (Lofthouse et al., 2012; Moriyama et al., 2012), knowledge about the neurocognitive effects of neurofeedback is limited. Therefore, the aim of this study was to investigate the additional effect of neurofeedback to TAU on neurocognitive functioning in adolescents with ADHD, within a multicenter parallel-randomized controlled trial design.

METHOD

Participants

Eligible participants were male adolescents with Dutch as their native language, between 12 and 24 years old, with a clinical DSM-IV-TR primary diagnosis of ADHD and a full-scale total intelligence quotient (TIQ) > 80 on the Wechsler Intelligence Scale for Children (WISC-III)(Wechsler, 1991) or the Wechsler Adult Intelligence Scale (WAIS-III).(Wechsler, 1997) Adolescents diagnosed with ASD (including: Autism, Asperger disorder and PDD-NOS) with confirmed symptoms of clinical ADHD - equal to a full ADHD diagnosis - were also included. Diagnosed ADHD symptoms were verified by a DSM-IV based Dutch semi-structured ADHD interview for adults (Kooij, 2002) and the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998; Sheehan et al., 1997). Trained psychologists administered the semi-structured interviews. Exclusion criteria were neurological disorders, schizophrenia and other psychotic disorders.

Initially, a total of 90 adolescents were randomized over the interventions: combined neurofeedback and TAU (NFB+TAU; n=59) or TAU (n=31). The dropout rate did not differ for NFB+TAU, n=14 (23.7%) and TAU, n=5(16.1%), p=.778 two-tailed Fisher exact test. At direct post-intervention analysis, NFB+TAU and TAU comprised n=45 and n=26 adolescents, respectively. The participant flow diagram is presented in Figure 1.

Medication use and presence of comorbid disorders were allowed. Comorbid disorders included: depressive disorders (4), anxiety disorders (2), substance related disorders (4), conduct disorders (4), learning disorders (6), communication disorders (1), tic disorders (1) elimination disorders (1), adjustment disorders (1), reactive attachment disorder (1). The final group characteristics are listed in Table 1.

Trial design

A multicenter parallel-group study was conducted, with stratification for age group (ages 12 through 15, 16 through 20, and 21 through 24 years) and imbalanced randomization (2:1) for NFB+TAU versus TAU. Randomization was computer-generated,(Dallal, 2007) with block lengths of 3, 6, 9 and 12 that varied randomly. An independent administrative employee was responsible for the assignment of participants to their groups immediately after pre-intervention assessment. The participant (and if applicable, his parents) was notified the same day whether he would receive neurofeedback intervention or not. Participants, parents, neurofeedback trainers, outcome assessor and clinical professionals were aware of the allocated group. The outcome assessor and neurofeedback trainer were not the same person. All data entry was performed blind to allocated intervention (NFB+TAU or TAU) and was checked twice by different research assistants.

Beforehand, a total sample size of 46 was calculated with G*power version 3.1.5.1(Faul, Erdefelder, Lang, & Buchner, 2007) to be sufficient to detect a medium effect size (f=.25) in a repeated measures ANOVA with an alpha .05 and a power of 90%. In this article, the CONSORT

2010 guidelines for reporting parallel group randomized trials were followed.(Schulz, Altman, & Moher, 2010) This trial is registered in the Dutch trial register (Ref. No.1759, http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=1759).

Interventions

Treatment as usual (TAU).

In the TAU group, the participants received treatment as prescribed by the main therapist of the participating center for child and adolescent psychiatry (GGzE, GGz Breburg, Reinier van Arkel group). TAU was monitored through an intervention questionnaire based on the "Dutch national basic program ADHD for children and adolescents"(Vink & Van Wamel, 2007). Behavioral interventions included cognitive behavioral therapy, systemic therapy and/or supportive counseling on a regular basis -at least once every two weeks, general session duration is 45 minutes-, either directed at the adolescent, *n*=26 (36.6%), and/or at the parent(s), *n*=20 (28.2%) (see Table 1). Stimulant medication use, *n*=35 (49.3%), included immediate release methylphenidate, sustained release methylphenidate or dexamphetamine. Atomoxetine was used by two participants at study entry. Because of the suggested similar clinical effects of stimulant medication and atomoxetine, in the analyses these two participants were categorized within the group of stimulant-medicated adolescents. Adherence to prescribed medication was verified by questioning the participants whether they took the prescribed medication. Stimulant medication use and received behavioral therapy did not differ between the group receiving TAU-only and the group who received neurofeedback in addition to TAU (see Table 1).

Neurofeedback in addition to TAU.

Neurofeedback training was carried out over a period of around 25 weeks, with two to three training sessions every week. Each participant was offered 40 training sessions of 30 minutes in total. The mean number of training sessions was 37 (36.98±4.94) with a minimum of 19 sessions. A neuropsychologist, EEG Biofeedback EEG Spectrum International Inc. certified, accredited by the Biofeedback Certification International Alliance (BCIA) (MB), trained the psychologists who gave the neurofeedback training.

Theta/SMR training (Lubar, 2003; Palsson, Pope, Ball, Turner, & Nevin, 2001, March) – a form of theta/beta training – was applied, with thresholds to inhibit theta/alpha frequency bands (4-7Hz and 8-11Hz), to reward SMR activity (13-15Hz) and inhibit beta/gamma (22-36Hz). Inhibition of the higher beta/gamma frequency band was conducted in this study to minimize the increase in SMR activity by increased muscle tension, and to decrease potential high beta that seems to occur in an estimated 10-20% of children with ADHD (Snyder & Hall, 2006). Training was conducted on Cz, referred to linked mastoids. The EEG signal was transmitted to the computer by the Brainquiry PET EEG 2 channel bipolar system:(Braininquiry) a DC amplifier with active electrodes, a low-pass anti-aliasing filter of 40Hz, a sample rate of 200Hz, and a 29-bit AD resolution. Neurofeedback training

was conducted with "EEGer" neurofeedback software version 4.2.1.(EEGer Spectrum Systems) The EEG signal was accordingly bandpass-filtered in the different frequency bands with an exponentially weighted moving average filter over 0.5 seconds to produce a short-term average. Each frequency band involved a 0.25Hz increment step size reward filter. Each training session was divided into ten 3-minute epochs. Artefact rejection thresholds for the raw EEG signal were set to 60μV. Relative thresholds for each frequency band were set to accept the signal 80 percent and to reject the signal 20 percent of the time. Thresholds were calculated to correspond to the mean amplitude in μV of each frequency band over the last 30 seconds of input and were calculated after 30 seconds from the beginning of each 3-minute part session. For the first 30 seconds, thresholds of former 3-minute session were preserved.

The trained frequency bands were represented in visual information to the participant on a screen by simple graphics. At the moment the signal for all frequency bands fulfilled all threshold criteria, auditory feedback was given by a short 0.25-second beep and the participants obtained a credit that increased the total session score.

Outcome measures

Primary outcome measures consisted of behavioral, neurocognitive, and electro-physiological measures. Behavioral measures included the DSM-IV based ADHD rating scale (Kooij et al., 2005), the Child Behavior Checklist (CBCL), and the Youth Self Report (YSR) (Achenbach, 1991).

Neurocognitive measures of sustained and selective attention, interference, concentration, working memory, and executive planning were applied. The d2 test of attention(Brickenkamp, 2007) was administered and the raw scores of the total number of processed items (TN) and total number of correctly processed items (C) were analyzed. Three digit spans backward (DSB) (Lezak, 2004; Wechsler, 1997) versions were constructed for the current study (see eAppendix 1) and applied alternately across the participants and the pre- and post-intervention assessments. Raw scores were computed for the total score – the amount correct recalled rows – and the amount of numbers of the longest recalled row. The Stroop color-word test (Hammes, 1978; Stroop, 1935) was applied; for analysis, raw scores of total execution time for the color-word card and the interference time – the difference in time between the color-word card and color card – were used. The Tower of London (TOL) (Culbertson & Zilmer, 2001, 2005) was applied according to the age of the participant: either the 7-15 years form or the 16+ years form. Raw scores used were the total correct score (tasks performed in the fewest number of moves possible), the total move score (number of moves, above the minimal required steps per task), initiation time (time before the first move), executive time (time from the first move to task completion), and total time (initiation time + executive time). TOL scores were summed scores over all ten tasks.

Procedure

Prior to the start of the study, approval was obtained from the medical ethics committee for mental health institutions in the Netherlands (Ref.no: NL 24776.097.08 CCMO). The study took place in three centers for child and adolescent psychiatry (GGzE, GGz Breburg, Reinier van Arkel group) in the South of the Netherlands. After the study was explained (verbally and in writing), written informed consent was obtained from each participant. For those younger than 18, parents also provided written informed consent.

At pre-intervention, participants were seen on three occasions for the administration of behavioral questionnaires, neurocognitive tests, the WAIS or WISC intelligence test, and electroencephalogram (EEG) measurements. In cases where participants were on medication, medication intake was also continued on the day of assessment.

Interventions took place between December 2009 and July 2012. Duration of the intervention period was approximately 25 weeks.

Post-intervention assessment included behavioral questionnaires and neurocognitive tests for all 71 participants.

Because of test administration problems, five participants were excluded for analysis of either the d2 test of attention, Stroop or TOL. One participant was excluded from analysis for the d2 test of attention, because of misinterpretation of the instructions at the second measurement. Two participants were excluded from analysis for the Stroop: one because he refused to cooperate with the test and the other because of a broken timer. For one participant, a version of the TOL, which was not age appropriate, was mistakenly administered and he was therefore excluded from further analysis.

Statistical analysis

All analyses were performed using SPSS version 21. Effects were considered significant if $p<.05$. Differences on group characteristics were analyzed with a one-way ANOVA or a chi-square test (χ^2) with Fisher exact correction. Attrition analyses compared the analyzed subsample to the total sample on group characteristics, behavioral and neurocognitive measures with a one-way ANOVA.

A Generalized Linear Model (GLM) ANOVA was applied for all the primary neurocognitive outcome measures with intervention group as between-subjects factor and time (e.g. between pre-intervention[t1] and post-intervention[t2]) as within-subjects factor. The full factorial models were tested. All neurocognitive effects were evaluated using multivariate test criteria. Effect sizes are expressed in percentage of explained variance in partial $\eta 2(\eta_p^2)$. In addition, the adjusted difference at post-intervention (AD_{t2-t1}) and 95% confidence interval (95% CI) were reported. Post hoc analyses were performed with separate addition of stimulant medication use at pre-intervention and diagnostic group (ADHD or ASD with comorbid ADHD) as between factor to the GLM.

Figure 1: *Participant Flow Diagram*

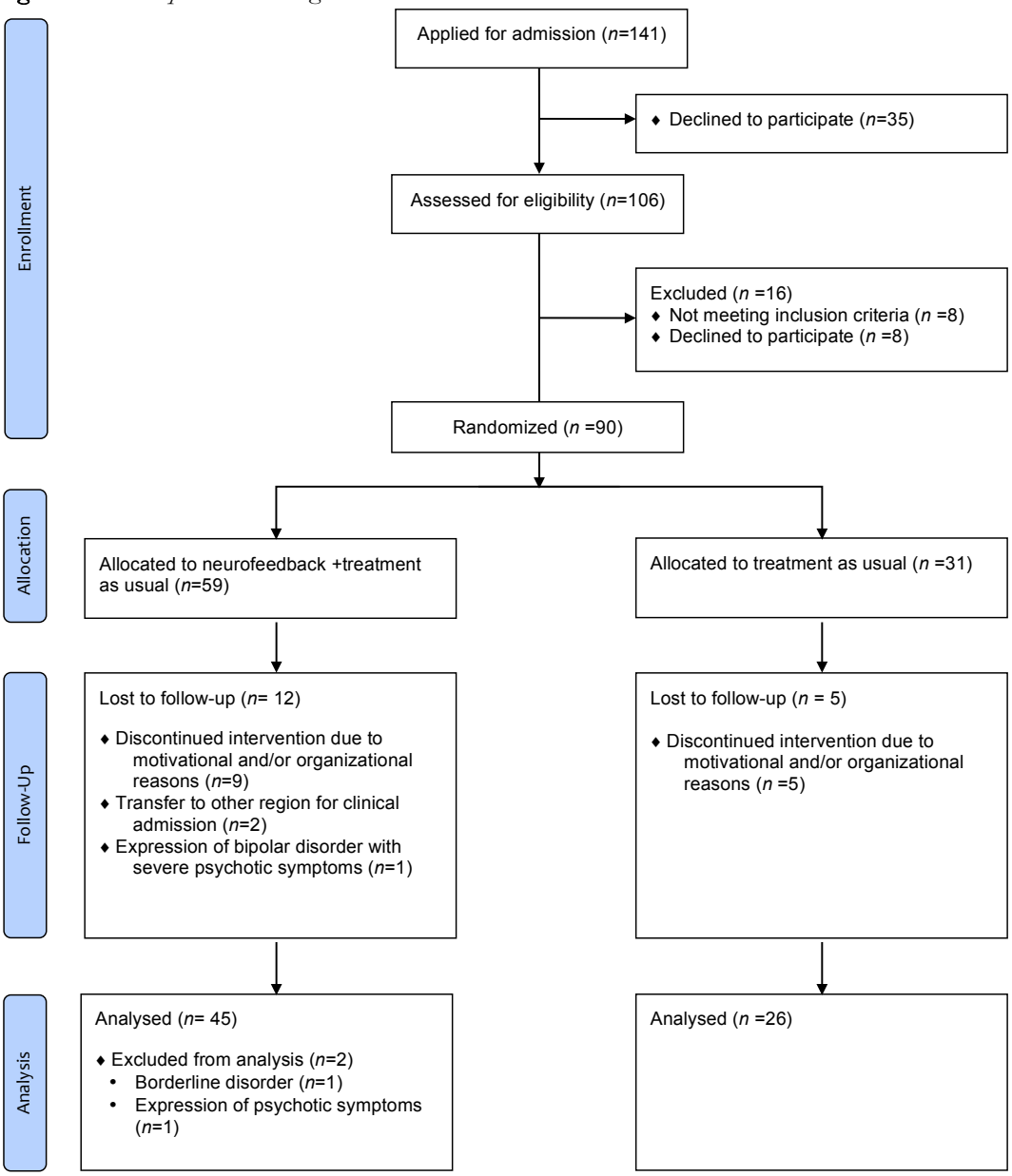

Table 1. Group characteristics and treatment as usual[a]

	TOTAL N=71	NFB+TAU *n*=45	TAU *n*=26	F	p
Age in Years (SD)	16.1(3.3)	16.1(3.3)	16.2(3.4)	.0	.864
DSM-IV-TR					
Diagnosis ADHD (%)	47(66.2)	29(64.4)	18(69.2)		.797
Diagnoses ASD+ ADHD (%)	24(33.8)	16(35.6)	8(30.7)		.797
GAF-scores (SD)	54.7(6.7)	53.8(7.1)	56.2(5.95)	2.0	.157
Treatment as usual					
Stimulant Med Pre-Intervention t1 (%)	35(49.3)	20(44.4)	16(61.5)		.220
Mean doses in mg (SD)[b]	37.2(16.4)	36.1(17.1)	38.6(15.9)	.2	.647
Months of intake before t1				3.7	.457
Up to 3 months (%)	6(8.5)	4(8.9)	2(7.7)		
3 to 6 months (%)	3(4.2)	2(4.4)	1(3.8)		
6 to 12 months (%)	4(5.6)	3(6.7)	1(3.8)		
12 months or longer (%)	23(32.4)	11(24.4)	12(46.2)		
Stimulant free (%)	35(49.3)	25(55.6)	10(38.5)		
Stimulant Med Started after t1 (%)	6(8.5)	3(6.7)	3(11.5)		.662
Stimulant Med Stopped after t1 (%)	9(12.7)	5(11.1)	4(15.4)		.716
Behavioral Interventions Adolescent[c] (%)	26(36.6)	14(31.1)	12(46.2)		.318
Behavioral Interventions Parent[c] (%)	20(28.2)	12(26.6)	8(30.7)		.787
Behavioral measures					
MINI ADHD Inattention (SD)	5.6(2.6)	5.4(2,6)	6.1(2.7)	1.2	.280
MINI ADHD H/I (SD)	4.0(2.5)	4.2(2.6)	3.7(2.3)	.5	.489
ADHD rating scale					
Inattention Childhood Symptoms[d] (SD)	6.1(2.7)	5.7(2.9)	6.8(2.0)	2.9	.093
H/I Childhood Symptoms[d] (SD)	4.9(2.9)	4.6(3.0)	5.6(2.6)	2.0	.160
Inattention Current Symptoms (SD)	4.7(2.4)	4.4(2.5)	5.3(2.2)	2.2	.142
H/I Current Symptoms (SD)	3.4(2.1)	3.4(2.1)	3.3(2.5)	.1	.734
YSR Total problem score (SD)	49.7(20.9)	48.0(22.0)	52.6(18.9)	.8	.382
YSR Attention problems (SD)	9.6(3.3)	9.4(3.32)	9.9(3.2)	.5	.487
CBCL Total problem score[e](SD)	62.3(27.6)	61.1(28.0)	64.1(27.3)	.2	.662
CBCL Attention problems[e] (SD)	11.5(3.4)	11.2(3.7)	12.0(3.1)	.9	.359
Intelligence					
IQ Discrepancy profile[f] (%)	24(33.8)	14(31.1)	10(38.5)		.606
Total IQ (SD)	100.7(11.3)	98.6(10.4)	104.2(12.2)	4.2	.045
Verbal IQ (SD)	102.4(12.9)	100.2(11.4)	106.2(14.5)	3.8	.057
Performance IQ (SD)	99.5(11.9)	98.4(11.2)	101.3(13.1)	1.0	.327

Note: [a]Data are means (SD) or numbers (%), t1 is pre-intervention, *df*(1,69); [b]mean doses in mg calculated for the adolescents on stimulant medication (*n*=35); [c]Behavioral interventions followed between pre- and post-intervention (t1-t2) as followed by the adolescents or one of the parents respectively; [d]Retrospective self-reported childhood symptoms (primary school period) and current symptoms (in the past 6 months); [e]CBCL data; total N=66 participants, NFB+ (*n*=40) and TAU (*n*=26), *df*(1,64); [f]IQ Discrepancy profile is considered as a profile with a difference score between VIQ and PIQ of 15 points or more. Because of the discrepancy profiles VIQ and PIQ are noted separately.

Abbreviations: NFB= neurofeedback, TAU= treatment as usual, DSM= Diagnostic and Statistical Manual, ADHD= attention deficit/hyperactivity disorder, ASD= autism spectrum disorder, GAF= Global Assessment of Functioning, Med: medication, MINI= Mini International Neuropsychiatric Interview, H/I = hyperactivity/impulsivity, YSR= Youth Self Report, CBCL= Child Behavior Checklist, IQ= Intelligence Quotient, VIQ= Verbal IQ, PIQ= performance IQ

RESULTS

Group Characteristics

At pre-intervention there were no differences for group characteristics, behavioral and neurocognitive primary outcome measures between the NFB+TAU group and the TAU group (Table 1). The only exception was TIQ: although TIQ for both groups was within the average range [95-105], TIQ was higher for the TAU group than for the NFB+TAU group.

Attrition Analysis

Attrition analysis showed that the dropout group (*n*=16), due to transfer, motivational and/or organizational reasons, did not differ from the total analyzed group (N=71) on group characteristics, behavioral and neurocognitive measures at pre-intervention. In addition, the subsamples of the d2 test of attention (*n*=70), Stroop (*n*=69) and TOL (*n*=70) did not differ from the total analyzed sample (N=71) on group characteristics, behavioral and neurocognitive measures at pre-intervention.

Neurocognitive measures

Neurocognitive outcome measures are summarized in Table 2. On the d2 test of attention, there was a large improvement over time for the adolescents on attention and/or motor speed, with more processed items and more correct processed items over the whole test. The DSB showed a medium improvement in attention for the adolescents with an increased total score over time. On the other hand, working memory, as estimated with the longest recalled row, did not change over time. Medium improvements were found on the Stroop, with shorter executive and interference times at post-intervention. Similarly, the TOL revealed a medium improvement with shorter executive and total times. However, planning as estimated with the total move score, total correct score and initiation time revealed no improvement over time. Neurocognitive measures were similar for the NFB+TAU and the TAU group and did not differ between the groups over time.

Post hoc analyses for stimulant medication use and ASD.

Stimulant-medicated adolescents did not differ over time from stimulant-free adolescents on the neurocognitive measures. Likewise, there were no differences over time on neurocognitive measures between adolescents with ADHD or combined ASD with ADHD.

Table 2. Raw scores pre- and post-intervention on the D2 test of attention, Digit Span Backwards, Stroop, and Tower of London

	Pre-Intervention (t1)		Post-Intervention (t2)		Adjusted difference	ANOVA			ANOVA			Post-hoc			Post-hoc		
	NFB+TAU	TAU	NFB+TAU	TAU	[95% CI] at Post-Intervention (t2-t1)	Time (t1 to t2)[a]			NFB+TAU and TAU over Time[a]			Med. Use over Time[b]			ASD+ADHD and ADHD over Time[b]		
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)		F	η_p^2	p	F	η_p^2	p	F	η_p^2	p	F	η_p^2	p
D2 test of attention	n=44	n=26	n=44	n=26													
TN	400.1(64.5)	421.3(68.9)	452.8(77.2)	457.6(73.9)	44.5[32.3, 56.6]	53.1	.44	*.000*	1.8	.03	.184	2.2	.03	.139	.2	.00	.632
C	158.6(25.8)	161.8(25.9)	179.5(32.3)	182.2(29.0)	21.6[16.8, 26.4]	80.7	.54	*.000*	.3	.00	.605	.6	.01	.456	.3	.00	.614
DSB	n=45	n=26	n=45	n=26													
Total score	6.5(1.6)	6.7(2.0)	6.7(1.6)	7.6(2.3)	.6[.1, 1.0]	6.9	.09	*.010*	2.2	.03	.140	.2	.00	.642	.2	.00	.627
Longest row	4.7(.9)	5.0(1.0)	4.8(.9)	5.2(1.3)	.2[-.1, .4]	1.3	.02	.250	.3	.00	.608	.2	.00	.675	.0	.00	.906
Stroop[c]	n=43	n=26	n=43	n=26													
Color/word card	99.8(22.6)	99.4(25.7)	91.9(20.4)	95.9(32.4)	-6.1[-10.7, -1.5]	7.0	.09	*.010*	.6	.01	.454	3.0	.04	.087	1.7	.03	.201
Interference	34.7(14.4)	35.2(18.1)	30.2(12.9)	30.5(19.9)	-4.5[-8.5, -.7]	5.4	.08	*.023*	.0	.00	.979	3.0	.04	.086	2.3	.03	.137
TOL	n=45	n=25	n=45	n=25													
Correct score	3.5(1.8)	3.6(1.6)	3.2(1.9)	4.3(2.1)	.2[-.3, .7]	.7	.01	.401	3.2	.05	.077	2.4	.03	.129	.0	.00	.983
Move score	31.5(16.0)	32.9(13.6)	31.4(16.3)	28.5(15.3)	-2.3[-6.4, 1.9]	1.2	.02	.277	1.1	.02	.297	.1	.00	.710	.0	.00	.729
Initiation Time	23.3(16.6)	20.1(10.2)	22.6(21.5)	22.7(12.2)	-.9[-2.3, 4.2]	.3	.00	.574	1.0	.01	.322	.5	.01	.485	2.5	.04	.117
Execution Time	174.7(71.0)	173.5(50.3)	144.8(40.2)	151.4(51.8)	-26.0[-41.6, -10.4]	11.1	.14	*.001*	.2	.00	.624	.1	.00	.713	.1	.00	.816
Total Time	198.0(77.1)	193.6(52.4)	167.4(45.7)	174.0(52.6)	-25.1[-41.5, -8.7]	9.3	.12	*.003*	.4	.00	.507	.0	.00	.832	.3	.00	.592

Note: *=p<.05, **=p<.005, ***=p<.001; [a]Time from pre- to post-intervention; D2 test of attention *df*(1,68); DSB df (1,69); Stroop *df*(1, 67) ;TOL *df*(1,68), [b]Post hoc addition for medication use and ASD separately; D2 test of attention *df*(1,66); DSB *df*(1,67); Stroop *df*(1,65) ;TOL *df*(1,66). No interaction effects were found for time, intervention group, and stimulant medication use. [c]Time in seconds; Abbreviations: NFB= neurofeedback, TAU= treatment as usual, 95%CI= 95% Confidence Interval, ANOVA= Analysis of Variance, ASD= autism spectrum disorder, ADHD= attention deficit/hyperactivity disorder, TN= total number of processed items, C= total number of correctly processed items, DSB= Digit Span Backwards, TOL=Tower of London

DISCUSSION

The present study examined the additional value of neurofeedback to TAU on neurocognitive functioning in adolescents with ADHD, using a multicenter parallel-randomized controlled trial design. Results showed an improvement in neurocognitive measures of attention and/or motor skills at post-intervention for all adolescents with ADHD. Adolescents needed less time to process information and performed tasks with the same accuracy. Working memory and planning estimations remained stable over time.

Neurocognitive functioning improved as much for the adolescents who received neurofeedback in addition to the TAU as for the adolescents who received only TAU. The neurocognitive outcomes are in agreement with the behavioral outcomes of the current study that showed large improvements on parent as well as on self-reported behavior irrespective of treatment allocation. This is in line with results from two double-blind studies with children with ADHD that also failed to find more improvement on behavioral questionnaires (Arnold et al., 2012; van Dongen-Boomsma et al., 2013) and neurocognitive measures (Arnold et al., 2012; Vollebregt et al., 2013) for neurofeedback over sham-neurofeedback. Furthermore, a study in healthy students who scored relatively high on ADHD symptoms found similar results for neurofeedback and sham-neurofeedback on self-reported attention problems as well as RT and accuracy (Logemann et al., 2010). In contrast, positive results were shown in a study with better performance for neurofeedback compared to EMG biofeedback on RT and accuracy in children with ADHD (Bakhshayesh et al., 2011).

The differences in outcomes of the studies might be a result of the applied training protocol. The RCT studies that failed to find significant effects for neurofeedback in the treatment of ADHD (Arnold et al., 2012; Logemann et al., 2010; van Dongen-Boomsma et al., 2013), like the current study, combined inhibition of theta with reward of SMR (12-15Hz) activity in the majority of the applied (sometimes individualized) training protocols. In contrast, the neurofeedback versus EMG biofeedback study of Bakhshayesh et al. (2011) applied a somewhat different protocol with also inhibition of theta, but reward of beta (16-20Hz) instead of SMR activity. Similarly, reward of the higher beta (16-20Hz) range in the training protocol was also applied in the study of Gevensleben, Holl, Albrecht, Vogel, et al. (2009) that showed neurofeedback to be more effective in reducing ADHD symptoms than computerized attention training, and in the studies that compared neurofeedback to stimulant medication (Duric et al., 2012; Meisel et al., 2013). It might be that training protocols aimed at (also) rewarding beta (16-20Hz) are more favorable in the training of attention. However, at this moment training protocols are used alternately in clinical practice as well as in research. There is no consensus on the exact kind of protocol to apply for the treatment of ADHD. Therefore, additional knowledge about specific working mechanisms of neurofeedback on the brain is necessary before neurofeedback protocols can be adapted appropriately for the treatment of psychiatric disorders.

Stimulant-medication use by the participants was allowed in the current study as a part of TAU. Therefore, it could be hypothesized that medication could have mediated the effect of neurofeedback. Overall, stimulant-medication improves neurocognitive functioning (Coghill et al.). It could be that the magnitude of the improvement depends on the cognitive domain. Task improvements by stimulant medication were seen especially in less cognitive demanding repetitive tasks that need sustained attention as RT variability and less in more complex cognitive tasks (Swanson, Baler, & Volkow, 2011). Comparably, the current study shows improvement over time in measures of attention and processing speed and not in more complex cognitive tasks. However, we did not find the expected better performance in stimulant-medicated adolescents compared to stimulant-free adolescents. The long-term effects of stimulant-treatment on neurocognitive functioning are less well known (Swanson et al., 2011). Three-quart of the adolescents who used stimulant medication started intake 6-months or longer before study entrance. Consequently, this long-term intake of stimulant medication might contribute to the absence of differentiation by stimulant medication use.

Although neurofeedback does not seem effective for autism symptoms, a review indicated it could be effective for comorbid ADHD symptoms in ASD (Holtmann et al., 2011). Therefore, adolescents with clinical ADHD symptoms and ASD were also included in the current study. None of the outcomes differentiated between adolescents with ADHD versus combined ASD and ADHD; both diagnostic groups showed similar improvements over time. This suggests that the co-occurrence of ASD did not influence the outcomes.

The present study contributes to the literature by applying an RCT design in a naturalistic multimodal treatment setting, thereby increasing the ecological validity of the study. However, as a consequence, the target population consisted of a heterogeneous group of male adolescents with complex problems. Previous research that showed positive results on measures of attention (Gevensleben, Holl, Albrecht, Vogel, et al., 2009) was based on more homogeneous populations with ADHD. Another point of consideration is that the current study included adolescents who were older than the children in previous research. Studies that revealed positive results all aimed at children with a mean age of around ten years, whereas the mean age of the participants was sixteen years in the current study. Developmental related large increases in attention and/or (motor) speed during adolescence (Gur et al., 2012) might have induced ceiling effects on the neurocognitive tests. Furthermore, practice effects by multiple testing are known to have a considerable impact on test outcomes (Calamia, Markon, & Tranel, 2012). Consequently, outcomes might reflect practice effects rather than improved neurocognitive functioning. In addition, TIQ was somewhat higher for the TAU group than the NFB+TAU group. As a result, it could be assumed that with a higher TIQ, practice effects could be larger (Calamia et al., 2012) and could conceal potential treatment effects in the NFB+TAU group. Diminished and improved learning curves have indeed been found in low and high average TIQ respectively (Rapport, Axelrod, et al., 1997; Rapport, Brines, Theisen, & Axelrod, 1997). Note, that both intervention groups had a mean TIQ within the average range [95-105] and did not differ significant on any of the other measures, including PIQ. Therefore, we consider the impact of the

difference is likely to be minimal. Overall, the large improvement over time might reflect practice effects, developmental changes, learning effects, as well as effects of TAU.

In conclusion, NFB+TAU and TAU both showed significantly improved neurocognitive outcomes – mainly processing speed – at post-intervention. No additional value of neurofeedback over TAU was found. Hence, this study does not provide evidence for using theta/SMR neurofeedback to enhance neurocognitive performance as additional intervention to TAU for adolescents with ADHD and comorbid disorders in clinical practice.

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CHAPTER 7

One-Year Follow-Up of Neurofeedback in Adolescents with ADHD: A Randomized Controlled Trial

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ABSTRACT

Background: Neurofeedback is proposed as an effective treatment for reduction of Attention Deficit Hyperactivity Disorder (ADHD) symptoms. Therefore, long-term additional effects of neurofeedback compared to treatment as usual (TAU) for adolescents with ADHD were investigated. **Methods**: Using a multicenter parallel-randomized controlled trial design, 90 adolescents with a DSM-IV-TR diagnosis of ADHD, were randomized and stratified for age group (ages 12 through 15 years, 16 through 20 years, and 21 through 24 years) to receive either a combination of neurofeedback and TAU (NFB+TAU) or TAU. Neurofeedback treatment consisted of approximately 37 sessions of theta/SMR-training on Cz. Sixty adolescents receiving NFB+TAU (*n*=41) or TAU (*n*=19), (age M=15.95 years, SD=3.33), were followed for one year after the treatment period. Outcome measures at follow-up included behavioral self-reports (MINI, ADHD rating scale, YSR) and neurocognitive measures (d2 attention test, digit span backward, Stroop test, Tower of London test). Data were collected between December 2009 and August 2013. **Results**: Behavioral problems decreased from pre-intervention to one-year follow-up for both groups. Adjusted differences [95% confidence intervals] for attention problems were MINI: -1.38[-2.04 to -.72], ADHD rating scale: -1.64[-2.24 to -1.03] and YSR: -2.23 [-3.09 to-1.37]. At follow-up adolescents' performance of the neurocognitive tasks was faster irrespective of treatment group. **Conclusions**: Overall, TAU was as effective as NFB+TAU for adolescents with ADHD symptoms. Given the absence of robust additional long-term effects in the current study, it is questionable whether theta/SMR neurofeedback should be used to treat adolescents with ADHD and comorbid disorders. **Clinical Trials Registration:** This trial is registered in the Dutch trial register (Ref. No.1759, http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=1759).

INTRODUCTION

Attention Deficit/Hyperactivity Disorder (ADHD) is characterized by re-occurring patterns of inattention and/or hyperactivity-impulsivity (HI) symptoms that interfere with developmentally appropriate social, academic, or occupational functioning (American Psychiatric Association, 2000). Neurodevelopmental conditions like learning disabilities, conduct disorder, depression and anxiety are seen more often in youngsters with ADHD than in youngsters without ADHD (Larson, Russ, Kahn, & Halfon, 2011). In addition, it is estimated that around one third to half of youngsters with autism spectrum disorders (ASD) display ADHD comorbidity (Gjevik, Eldevik, Fjaeran-Granum, & Sponheim, 2011; Simonoff et al., 2008). Stimulant medication and behavioral therapy are considered the treatments of choice for ADHD. Stimulant medication is effective in reducing ADHD symptoms in youngsters with ADHD (Faraone & Buitelaar, 2010; Greenhill et al., 2001) and - although possibly to a lesser extent - in youngsters with combined ADHD and ASD (Cortese, Castelnau, Morcillo, Roux, & Bonnet-Brilhault, 2012; Research Units on Pediatric Psychopharmacology (RUPP) Autism Network, 2005). Although medication seems to be effective, there are some noteworthy limitations, namely that knowledge of the long-term and side-effects of stimulant medication is limited (van de Loo-Neus, Rommelse, & Buitelaar, 2011). Moreover, despite the persistent nature of ADHD, the majority of adolescents with ADHD discontinues stimulant medication before adulthood (McCarthy et al., 2012; Zetterqvist, Asherson, Halldner, Langstrom, & Larsson, 2013). Additions or alternatives to the current treatment as usual (TAU) to reduce ADHD symptoms further, and on a long-term basis, are therefore desirable. Neurofeedback has been suggested as a potentially effective intervention for reducing ADHD symptoms (Lofthouse, Arnold, Hersch, Hurt, & DeBeus, 2012; Moriyama et al., 2012) and ASD (Holtmann et al., 2011).

Neurofeedback is intended to alter brain activity by providing feedback from electroencephalogram (EEG) activity to patients; this is expected to lead to improvements in behavior. Overall, youngsters with ADHD show increased theta (Cortese, 2012; Loo & Makeig, 2012; Snyder & Hall, 2006), and decreased beta (Cortese, 2012; Snyder & Hall, 2006) activity compared to typical developing (TD) youngsters. Increased theta (4-7Hz) is associated with lower vigilance and decreased beta (13-30Hz) is associated with reduced attention (Banaschewski & Brandeis, 2007). In addition, beta activity (12-20Hz) has been related to behavioral inhibition (Sterman & Wyrwicka, 1967), specifically, low beta activity measured above the central sulcus - also referred to as the sensorimotor rhythm (SMR; 12-16Hz) (Roth, Sterman, & Clemente, 1967; Sterman & Wyrwicka, 1967; Sterman, Wyrwicka, & Roth, 1969). As neurofeedback aims to reduce ADHD symptoms such as diminished vigilance, attention and inhibition, most neurofeedback protocols include training to suppress theta activity and reinforce beta (12-20Hz) or SMR (12-15Hz) with electrode placement on Cz (Lofthouse et al., 2012; Loo & Makeig, 2012; Moriyama et al., 2012). A complete neurofeedback intervention typically comprises 20 to 40 training sessions (Loo & Makeig, 2012).

Estimates of the effectiveness of neurofeedback for the treatment of ADHD depend on the study design. The most stringent double-blind studies have failed to find that neurofeedback is

superior to placebo neurofeedback for the reduction of ADHD symptoms assessed by behavioral (Arnold et al., 2013; van Dongen-Boomsma, Vollebregt, Slaats-Willemse, & Buitelaar, 2013) or neurocognitive measures (Vollebregt, van Dongen-Boomsma, Buitelaar, & Slaats-Willemse, 2013). A single-blind study did find that children who received neurofeedback showed a greater improvement in attention on the basis of parental report, and reaction time and accuracy on neurocognitive tests than children who received electromyography (EMG) biofeedback (Bakhshayesh, Hansch, Wyschkon, Rezai, & Esser, 2011). However, none of the blind studies looked at the long-term effects of neurofeedback. Long-term effects of neurofeedback were found in two randomized controlled trials (RCT): neurofeedback was more effective in reducing ADHD symptoms as reported by parents than computerized attention training up to six months post-treatment (Gevensleben et al., 2010; Steiner, Frenette, Rene, Brennan, & Perrin, 2014). Two further RCT studies found that neurofeedback was as effective as stimulant medication (Duric, Assmus, Gundersen, & Elgen, 2012; Meisel, Servera, Garcia-Banda, Cardo, & Moreno, 2013). Conversely, another RCT found that stimulant medication but not neurofeedback decreased ADHD symptoms (Ogrim & Hestad, 2013). To date there has been only one study comparing the long-term effects of stimulant medication and neurofeedback (Meisel et al., 2013). This study used a naturalistic follow-up at 6 months, and at follow-up the level of ADHD symptoms was similar for children who had received neurofeedback (n=12) and children treated with stimulant medication (n=11).

In summary, neurofeedback is viewed as a possible treatment for ADHD symptoms. Comparative studies of effectiveness have shown that neurofeedback training can be as effective as stimulant medication or a combination of stimulant medication and neurofeedback (Duric et al., 2012), but evidence on the long-term effects of neurofeedback is limited. Since the aim of neurofeedback is to induce enduring changes in brain regulation in order to improve behavior, one would predict long-term effects as a consequence of improved brain functioning. The aim of the current study was therefore to investigate the value of neurofeedback as a supplement to TAU for adolescents with ADHD and comorbid disorders at one-year follow-up.

METHODS

Participants

Eligible participants were male adolescents with Dutch as their native language, between 12 and 24 years old, with a primary clinical DSM-IV-TR (American Psychiatric Association, 2000) diagnosis of ADHD and a full-scale total intelligence quotient (TIQ) >80 on the Wechsler Intelligence Scale for Children (WISC-III) or the Wechsler Adult Intelligence Scale (WAIS-III) (Wechsler, 1991, 1997). Adolescents diagnosed with ASD (autism, Asperger's syndrome or pervasive developmental disorder - not otherwise specified; PDD-NOS) with confirmed clinical ADHD symptoms sufficient for a clinical diagnosis were also included. ADHD symptoms were verified by a Dutch semi-structured DSM-IV-based ADHD interview for adults (Kooij, 2002) and the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998; Sheehan et al., 1997). Exclusion criteria were neurological disorders, schizophrenia and other psychotic disorders.

In total 90 adolescents were randomly assigned to the treatment groups: combined neurofeedback and TAU (NFB+TAU; n=59) or TAU only (TAU; n=31). The total dropout and exclusion rate after randomization did not differ for NFB+TAU, n=18 (30.5%) or TAU, n=12 (38.7%), p=.485 two-tailed Fisher exact test. For the one-year follow-up analysis the group sizes were NFB+TAU: n=41 and TAU: n=19. The participant flow diagram is presented in Figure 1.

Medication use and comorbid disorders were allowed. Comorbid disorders present in the final group at one-year follow-up: depressive disorders (1), anxiety disorders (3), substance-related disorders (3), conduct disorders (3), learning disorders (5), tic disorders (1), reactive attachment disorder (1). The final group characteristics are listed in Table 1.

Trial design

A multicenter parallel group study was conducted, with stratification for age group (12 through 15 years, 16 through 20 years, and 21 through 24 years) and unbalanced randomization to treatment (2 NFB+TAU: 1 TAU). The randomization process was computer-controlled (Dallal, 2007), using randomly varying block lengths of 3, 6, 9 and 12. An independent administrative employee was responsible for the assignment of participants to the treatment groups immediately after pre-intervention assessment. The participant (and if applicable, his parents) was notified the same day whether he would receive neurofeedback treatment. Participants, parents, neurofeedback trainers, the outcome assessor and clinical professionals were aware of group allocations. The roles of outcome assessor and neurofeedback trainer were fulfilled by different individuals. All data entry was blind to group allocation (NFB+TAU or TAU) and was checked twice by different research assistants.

Prior to the study we used G*power version 3.1.5.1 (Faul, Erdefelder, Lang, & Buchner, 2007) to calculate that a total sample size of 46 would be sufficient to detect a medium effect size (f=.25) in a repeated measures ANOVA with two measurements, with an alpha of .05 and a power of 90%. Where three measurements (pre-intervention, post-intervention and one-year follow-up) were available a total

sample size of 36 was predicted to be adequate to detect a similar effect size. We have followed the CONSORT 2010 guidelines (Schulz, Altman, & Moher, 2010) for reporting parallel group randomized trials. This trial is registered in the Dutch trial register (Ref. No.1759, http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=1759).

Interventions

Treatment as usual (TAU*)*

In the TAU group, the participants received treatment as prescribed by the main therapist in the participating centers for child and adolescent psychiatry (GGzE, GGz Breburg, Reinier van Arkel group). The TAU group was monitored using an intervention questionnaire based on the *Dutch national basic program ADHD for children and adolescents (Vink & Van Wamel, 2007)*. Behavioral interventions included regular (at least once every two weeks, typical session duration: 45 minutes) cognitive behavioral therapy, systemic therapy and/or supportive counseling for the adolescent and/or his parent(s) (see Table 1). Stimulants prescribed included immediate release methylphenidate, sustained release methylphenidate and dexamphetamine. Two participants were taking atomoxetine at study entry; one participant had changed to sustained released methylphenidate by the time of the one-year follow-up, the other participant continued to use atomoxetine through one-year follow-up. Because the clinical effects of stimulant medication and atomoxetine are suggested to be similar this participant was categorized as stimulant-medicated for the purposes of analysis at one-year follow-up. Adherence to prescribed medication was verified by asking participants whether they took their prescribed medication. There were no group differences (TAU vs. NFB+TAU) in the use of stimulant medication or the type of behavioral therapy received (see Table 1).

Neurofeedback in addition to TAU

Neurofeedback training was carried out over a period of around 5 months (25 weeks), with 2 to 3 training sessions every week. Each participant was offered a total of 40 thirty-minute training sessions. The mean number of training sessions undertaken was 38 (37.73 ± 4.43) with a minimum of 19 sessions for the adolescents in the NFB+TAU group at one-year follow-up, n=41. A neuropsychologist (MB) who was certified by EEG Biofeedback EEG Spectrum International Inc. certified, accredited by the Biofeedback Certification International Alliance (BCIA) trained the psychologists who administered the neurofeedback training. Theta/SMR training (Lubar, 2003) – a form of theta/beta training – was used, with thresholds to inhibit theta/alpha frequency bands (4-7Hz and 8-11Hz), reward SMR activity (13-15Hz) and inhibit beta/gamma (22-36Hz). Inhibition of the higher beta/gamma was used to minimize the increase in SMR activity resulting from increased muscle tension and to decrease the high beta activity that occurs in an estimated 10-20% of children with ADHD (Snyder & Hall, 2006). Training was conducted on Cz, referenced to linked mastoids. The EEG signal was transmitted to computer by the Brainquiry PET EEG 2 channel bipolar system

(Braininquiry): a DC amplifier with active electrodes, a 40Hz low-pass anti-aliasing filter, a sample rate of 200Hz, and 29-bit AD resolution. Neurofeedback training was conducted with 'EEGer' neurofeedback software version 4.2.1 (EEGer Spectrum Systems). The EEG signal was bandpass-filtered in the different frequency bands and an exponentially weighted moving average (0.5 seconds) filter was used to produce short-term averages. Each frequency band had a 0.25Hz increment reward filter. Each training session was divided into 10 three-minute epochs. Artifact rejection thresholds for the raw EEG signal were set at 60μV. Relative thresholds for each frequency band were set to accept the signal of the particular frequency band 80% of the time and reject the signal 20% of the time. Thresholds corresponded to the mean amplitude in μV of each frequency band over the previous 30 seconds of input and were calculated 30 seconds after the start of each three-minute part session. For the first 30 seconds of a three-minute session, the thresholds from the previous three-minute session were used. The trained frequency bands were represented to the participant using simple graphics on a screen. Reinforcement was given when all frequency bands were within thresholds at the same moment, by auditory feedback -a 0.25s beep-, and an increase of the participant's session score.

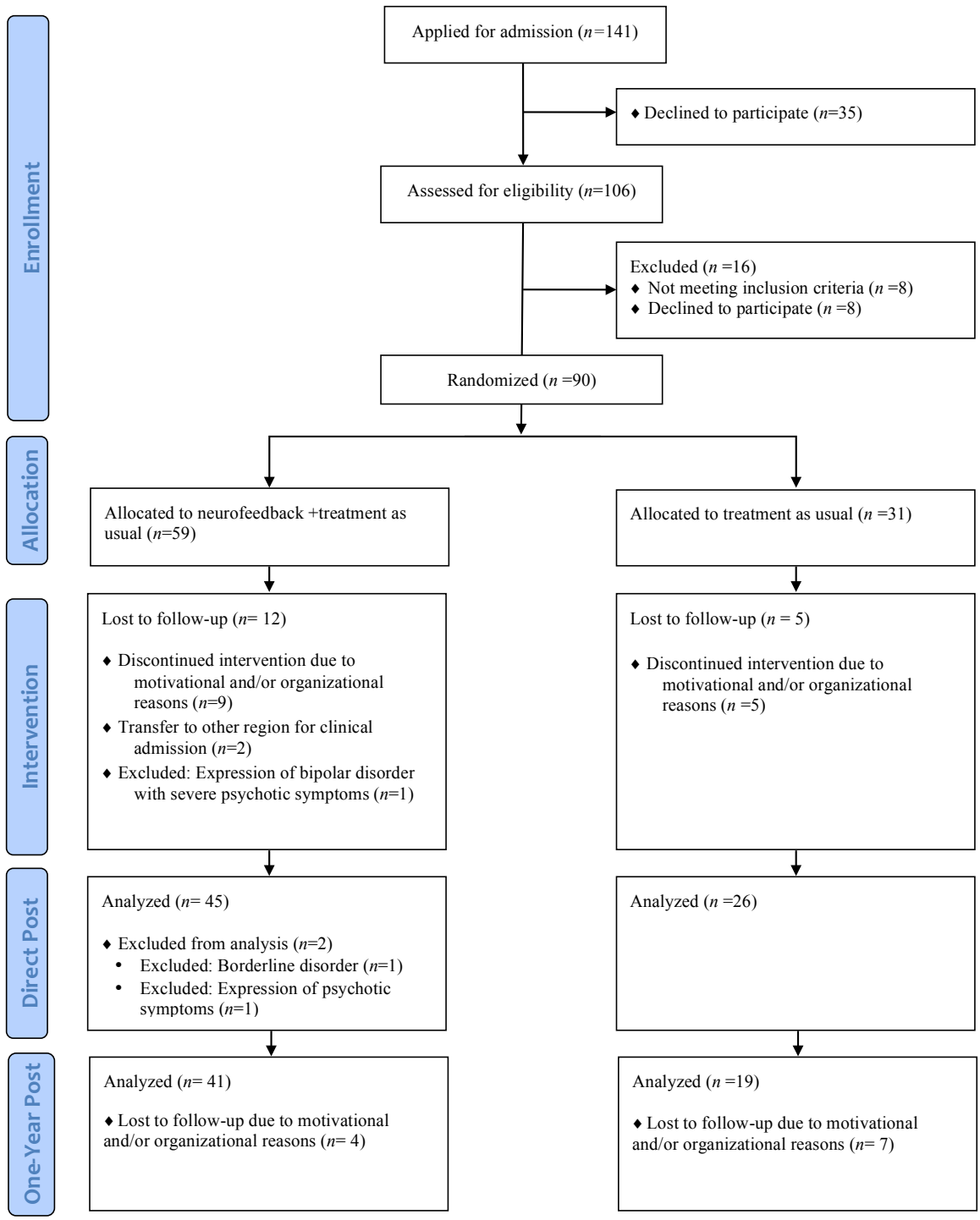
Outcome Measures

Outcome measures included three behavioral self-reports and four neurocognitive measures.

Behavioral measures: 1) The MINI (Sheehan et al., 1998; Sheehan et al., 1997) ADHD subscales for children and adolescents covering inattention and HI symptoms over the last six months (scale range: 0 to 9). 2) The ADHD rating scale, a DSM-IV-based self-report for adults (Kooij et al., 2008; Kooij et al., 2005), with subscales for inattention and HI (scale range: 0 to 9) (46,47). 3) The Youth Self Report (YSR) (Achenbach, 1991): the attention problems subscale, the externalizing problems scale and total problems scale were used. Participants aged over 18 years also completed the YSR, as most of them were still attending school and living with their parents.

Neurocognitive measures: 1) The d2 attention test (Brickenkamp, 2007) was administered and the raw scores for total processed items (TN) and total correctly processed items (C) were analyzed. 2) Three versions of the digit span backwards (DSB) (Lezak, 2004; Wechsler, 1997) were constructed for the current study and applied in turn across participants and assessments (pre-intervention, post-intervention and one-year-follow-up); total score (number of rows recalled correctly) and the maximum correctly recalled row length were used. 3) The Stroop color-word test (Hammes, 1978; Stroop, 1935), was administered; raw scores for color-word card total execution time and interference time (difference between execution times for color-word card and color card) were used. 4) The age appropriate form (7-15 years or 16+ years) of the Tower of London (TOL) test (Culbertson & Zilmer, 2001, 2005) was administered. The total correct (tasks performed in the minimum number of moves), total moves (number of moves in excess of the minimum required), initiation time (time to first move), execution time (time between first move and task completion), and total time (initiation time plus execution time) were calculated. TOL scores were the summed across all ten tasks.

Figure 1: *Participant Flow Diagram*



Procedure

Prior to the start of the study, approval was obtained from the Medical Ethics Committee for Mental Health Institutions in the Netherlands (Ref. no: NL 24776.097.08 CCMO). The study took place in three centers for child and adolescent psychiatry (GGzE, GGz Breburg, Reinier van Arkel group) in the south of the Netherlands. After the study was explained (verbally and in writing), written informed consent was obtained from each participant. For those younger than 18 years, parents also provided written informed consent.

At pre-intervention, participants were seen on three occasions for the administration of behavioral questionnaires, neurocognitive tests, the WAIS or WISC intelligence test, and electroencephalogram (EEG) measurements, where applicable medication was taken as normal on the day of assessment. Interventions took place between December 2009 and July 2012. The duration of the intervention period was approximately 25 weeks. Data collection continued until August 2013. Post-intervention and one-year follow-up assessments included behavioral questionnaires and neurocognitive tests for all 60 participants. There was missing data for the d2 attention test (2 participants), Stroop test (2 participants), TOL (1 participant) either because of administrative problems or because the participant refused to complete the task. Parent reports (CBCL and autism questionnaire (AQ)) were not included because of the low response rate (48%) of the total randomized sample at the follow-up measurements.

Statistical Analysis

All analyses were performed using SPSS version 19.0. Effects were considered significant at $p<.05$. Differences in group characteristics were analyzed with a one-way ANOVA or a chi-square test (χ^2) with Fisher's exact correction. Attrition analyses for behavioral data with smaller sample size than the total sample size due to missing or incomplete data were performed by comparing group characteristics and other pre-intervention primary behavioral measures for the analyzed subsample and the total sample using a one-way ANOVA.

A completion analysis was applied involving the participants who finished all assessments up to one-year after the intervention (including neurofeedback training, if applicable), in order to determine whether neurofeedback had additional value after completion of the training. The effect of neurofeedback training was investigated using a Generalized Linear Model (GLM) with between- and within-subjects factors. This analysis was used separately for all primary behavioral measures with treatment group as between-subjects factor and time (i.e. pre-intervention (T1), post-intervention (T2) and one-year follow-up (T3)) as within-subjects factor. The full factorial models were tested. All behavioral effects were evaluated using multivariate test criteria. The adjusted difference (AD) and 95% confidence interval [95% CI] for the total sample (NFB+TAU and TAU) were noted and if applicable, separate post-hoc analyses of NFB+TAU and TAU effects were performed. Significant

two-way between-group interactions were investigated with separate post-hoc GLM ANOVAs for the NFB+TAU and TAU groups with time as within-subjects factor.

To control for potential outcome bias of the drop-outs (*n*=27) after randomization post-hoc analyses were performed based on imputation with Last Observation Carried Forward (LOCF) for the total group as randomized with the exception of the three excluded participants (see also flowchart: Figure 1).

To determine whether changes over time were associated with stimulant medication use, post-hoc analyses were performed to look for three-way interactions involving stimulant medication use (stimulant-medicated and stimulant-free) at one-year follow-up as an additional between-subjects factor. To determine whether co-occurrence of ASD influenced the outcomes, possible three-way interactions were also explored with post-hoc analyses with diagnostic group (ADHD or ASD with comorbid ADHD) as an additional between-subjects factor. Significant three-way between-groups interactions were investigated with separate post-hoc GLM RM ANOVAs for both stimulant medication conditions (stimulant-medicated and stimulant-free).

RESULTS

Group Characteristics

There were no baseline differences for the participants who completed the study up to one-year post-treatment in group characteristics between the NFB+TAU group and the TAU group (Table 1). There were also no pre-intervention group differences on behavioral or neurocognitive measures.

There were no significant differences between the treatment groups in terms of stimulant medication use at pre-intervention or one-year follow-up. Mean doses of stimulant medication in mg did not change for the total group (*n*=60) between pre-intervention, M=19.45, SD=22.43 and one-year follow-up, M=18.88, SD=22.98. For those who used stimulant medication at one-year follow-up (*n*=30) a general increase in dose was observed from pre-intervention M=30.30, SD=23.16 to one-year follow-up M=37.75, SD=18.37, $AD_{T3\text{-}T1}$=8.81, 95%CI=[.69 to 16.93]. There were no significant interactions between time and treatment group for dosage. In addition, those who used stimulant medication at one-year follow-up (*n*=30) started stimulant medication M=32,97, SD=32.39, 95%CI=[20.87 to 45.06], months before one-year follow-up and did not differ between the treatment groups.

Attrition Analysis

Attrition analysis showed that the participants who dropped out for motivational or organizational reasons (*n*=27), did not differ from the completers group (*n*=60) in terms of group characteristics or behavioral measures at pre-intervention. In addition, the subsamples for the d2 attention test (*n*=58) and the Stroop test (*n*=57) did not differ from the completers sample (*n*=60) in terms of group characteristics, or behavioral and neurocognitive measures at pre-intervention.

Table 1: Group characteristics and treatment as usual[A]

	TOTAL N=60	NFB+TAU *n*=41	TAU *n*=19
Age in Years T1	15.95(3.33)	15.85(3.34)	16.16(3.40)
DSM-IV-TR			
Diagnosis ADHD	38(63%)	26(63%)	12(63%)
Diagnosis ASD+ADHD	22(37%)	15(37%)	7(37%)
GAF-scores	54.85(6.58)	53.93(6.46)	56.84(6.58)
Treatment as usual			
Stimulant Medication T1	31 (52%)	19 (46%)	12(63%)
Stimulant Medication T2	29(48%)	17(41%)	12(63%)
Stimulant Medication T3	30(49%)	19(46%)	11(58%)
Behavioral interventions[B]			
Adolescent T1-T2	22(37%)	13(32%)	9(47%)
Adolescent T2-T3	13(22%)	9(22%)	5(26%)
Adolescent T1-T3	26(43%)	16(39%)	10(53%)
Parent T1-T2	16(27%)	11(27%)	5(26%)
Parent T2-T3	6(10%)	5(12%)	1(5%)
Parent T1-T3	18(30%)	12(29%)	6(32%)
Childhood behavior			
ADHD-rating Inattention[C]	6.10(2.46)	5.85(2.74)	6.63(1.67)
ADHD-rating H/I[C]	4.83(2.80)	4.71(2.87)	5.11(2.69)
Intelligence			
Total IQ	101.12(11.51)	99.22(10.61)	105.21(12.57)

Note:[A] Data are means (SD) or numbers (%);T1= pre-intervention; T2= direct post-intervention; T3=one-year follow-up; [B]Behavioural interventions followed between pre- and post-intervention (T1-T2), between post-intervention and the one-year follow-up (T2-T3) and between pre-intervention and one-year follow-up (T1-T3). [C]ADHD-rating scale retrospective self-reported childhood symptoms for Inattention and Hyperactivity/Impulsivity (HI). Group characteristics did not differ between groups.

Behavioral Measures

Behavioral outcome measures are summarized in Table 2. All measures showed a reduction in reported problems over time: MINI inattention subscale (p<.001) and HI subscale (p=.009), ADHD inattention scale (p<.001) and HI scale (p=.006), and the YSR total problems scale (p<.001) and externalizing problems scale (p=.013). The reduction over time in attention problems measured by the YSR attention problems subscale (p<.001), followed a different time course in the NFB+TAU and TAU groups (p=.041). The NFB+TAU group showed a decrease in YSR attention problems from pre-intervention to one-year follow-up, $AD_{T3\text{-}T1}$=-2.20, 95%CI=[-3.14 to -1.25], as did the TAU group, $AD_{T3\text{-}T1}$=-2.26, 95%CI=[-3.85 to -.67]. The NFB+TAU group showed a decrease from pre-intervention to post-intervention, $AD_{T2\text{-}T1}$=-2.02, 95%CI=[-2.99 to-1.06]; but not between post-intervention and one-year follow-up, $AD_{T3\text{-}T2}$=-.17, 95%CI=[-.97 to .62]. However, the TAU group did not show a decrease between pre-intervention and post-intervention, $AD_{T2\text{-}T1}$=-.37, 95%CI=[-2.11 to 1.37]; but there was a decrease from post-intervention to one-year follow-up, $AD_{T3\text{-}T2}$ =-1.89, 95%CI=[-3.07 to .72].

Table 2: Behavioral measures[A]

Test				Pre-Intervention (T1)		Post-Intervention (T2)		One-Year Follow-Up (T3)		Adjusted Difference T3-T1[C]		Adjusted Difference T3-T2[C]	
	ITT[B]		*n*	*Mean*	*(SD)*	*Mean*	*(SD)*	*Mean*	*(SD)*	*AD*	*[95%CI]*	*AD*	*[95%CI]*
MINI[D]													
Inattention	Completers	NFB+TAU	*n=41*	5.46	(2.42)	n/a		4.12	(2.56)	-1.38	[-2.04 to -.72]	n/a	
		TAU	*n=19*	6.32	(2.60)	n/a		4.89	(2.74)				
	LOCF	NFB+TAU	*n=56*	5.46	(2.51)	n/a		4.48	(2.68)	-.93	[-1.39 to -.47]	n/a	
		TAU	*n=31*	5.77	(2.64)	n/a		4.90	(2.64)				
H/I	Completers	NFB+TAU	*n=41*	4.17	(2.64)	n/a		2.90	(2.30)	-.90	[-1.52 to -.27]	n/a	
		TAU	*n=19*	3.26	(2.13)	n/a		2.74	(2.33)				
	LOCF	NFB+TAU	*n=56*	4.16	(2.51)	n/a		3.23	(2.33)	-.63	[-1.05 to -.20]	n/a	
		TAU	*n=31*	3.71	(2.27)	n/a		3.39	(2.46)				
ADHD-rating[E]													
Inattention	Completers	NFB+TAU	*n=41*	4.63	(2.41)	2.95	(2.63)	2.73	(2.32)	-1.64	[-2.24 to -1.03]	-.08	[-.60 to .44]
		TAU	*n=19*	5.42	(2.04)	4.00	(2.31)	4.05	(2.84)				
	LOCF	NFB+TAU	*n*=56	4.43	(2.44)	3.14	(2.38)	3.04	(2.41)	-1.18	[-1.64 to -.72]	.25	[-.28 to .78]
		TAU	*n*=31	5.10	(2.14)	3.52	(2.38)	4.13	(2.62)				
H/I	Completers	NFB+TAU	*n=41*	3.56	(2.12)	2.49	(2.20)	2.05	(2.22)	-.97	[-1.57 to -.36]	-.22	[-.72 to .28]
		TAU	*n=19*	2.95	(1.87)	2.53	(2.39)	2.53	(2.27)				
	LOCF	NFB+TAU	*n*=56	3.48	(2.16)	2.82	(2.33)	2.29	(2.32)	-.79	[-1.22 to -.36]	-.74	[-1.23 to -.24]
		TAU	*n*=31	3.52	(2.14)	4.06	(2.72)	3.13	(2.50)				

Test				Pre-Intervention (T1)		Post-Intervention (T2)		One-Year Follow-Up (T3)		Adjusted Difference T3-T1[C]		Adjusted Difference T3-T2[C]	
	ITT[B]		*n*	*Mean*	*(SD)*	*Mean*	*(SD)*	*Mean*	*(SD)*	*AD*	*[95%CI]*	*AD*	*[95%CI]*
YSR[F]													
Attention	Completers	NFB+TAU	*n=41*	9.63	(3.18)	7.61	(3.51)	7.44	(3.46)	-2.23	[-3.09 to -1.37]	-1.03	[-1.73 to -.34]
		TAU	*n=19*	10.00	(3.18)	9.63	(3.73)	7.74	(3.62)				
	LOCF	NFB+TAU	*n*=56	9.32	(3.17)	7.75	(3.33)	7.63	(3.30)	-1.70	[-2.35 to -1.06]	-.64	[-1.12 to -.17]
		TAU	*n*=31	9.74	(3.13)	9.19	(3.38)	8.03	(3.28)				
Externalizing	Completers	NFB+TAU	*n=41*	16.00	(9.99)	13.80	(7.39)	12.95	(8.11)	-3.16	[-5.23 to -1.09]	-1.03	[-2.59 to .52]
		TAU	*n=19*	14.37	(8.19)	12.32	(8.08)	11.11	(7.10)				
	LOCF	NFB+TAU	*n*=56	16.39	(9.35)	14.68	(7.37)	14.05	(7.99)	-2.46	[-.3.89 to -1.20]	-.68	[-1.72 to .35]
		TAU	*n*=31	16.13	(8.71)	14.29	(9.16)	13.55	(8.85)				
Total	Completers	NFB+TAU	*n=41*	48.80	(22.50)	41.10	(18.17)	39.76	(20.72)	-12.26	[-17.66 to -6.86]	-4.75	[-9.14 to -.36]
		TAU	*n=19*	53.16	(20.61)	45.84	(20.17)	37.68	(18.56)				
	LOCF	NFB+TAU	*n*=56	49.25	(20.88)	42.91	(18.40)	41.93	(20.36)	-8.87	[-12.73 to -5.01]	-2.99	[-5.95 to -.04]
		TAU	*n*=31	51.84	(18.41)	46.42	(19.44)	41.41	(19.05)				

Note: [A] Data are means (SD),[B] Intention to treat (ITT), [C]Adjusted difference (AD) and 95% confidence interval [95%CI] between one-year follow-up minus pre-intervention are displayed for the total group (NFB+TAU and TAU), [D]MINI Inattention and H/I were only reported at pre-intervention (T1) and at one-year follow-up (T3), [E]ADHD-rating scale self-reported current symptoms for Inattention and Hyperactive/Impulsive (H/I), [F]YSR scales: Attention problems, Externalizing problems and Total problems.

Table 3: Neurocognitive measures[A]

Test				Pre-Intervention (T1)		Post-Intervention (T2)		One-Year Follow-Up (T3)		Adjusted Difference T3-T1[C]		Adjusted Difference T3-T2[C]	
	ITT[B]		*n*	*Mean*	*(SD)*	*Mean*	*(SD)*	*Mean*	*(SD)*	*AD*	*[95%CI]*	*AD*	*[95%CI]*
D2[D]													
Total processed items (TN)	Completers	NFB+TAU	*n=39*	397.79	(59.97)	451.00	(72.39)	473.33	(67.40)	64.22	[49.85 to 78.59]	23.83	[10.73 to 36.92]
		TAU	*n=19*	419.68	(64.89)	447.26	(82.86)	472.58	(82.17)				
	LOCF	NFB+TAU	*n=56*	408.98	(71.17)	450.34	(78.78)	466.95	(75.79)	51.95	[39.45 to 64.45]	16.06	[7.21 to 24.92]
		TAU	*n=31*	428.87	(72.94)	459.29	(74.94)	474.81	(72.94)				
Total correct processed items (C)	Completers	NFB+TAU	*n=39*	155.15	(22.77)	178.87	(29.21)	185.49	(27.39)	29.72	[23.72 to 35.72]	9.81	[3.94 to 15.68]
		TAU	*n=19*	162.79	(25.69)	178.89	(33.04)	191.89	(39.63)				
	LOCF	NFB+TAU	*n=56*	159.89	(30.480	177.88	(34.53)	183.20	(32.67)	24.18	[19.10 to 29.27]	6.65	[2.64 to 10.65]
		TAU	*n=31*	165.39	(29.41)	182.48	(30.57)	190.45	(34.70)				
DSB[E]													
Total score	Completers	NFB+TAU	*n=41*	6.51	(1.63)	6.85	(1.56)	6.88	(2.08)	.60	[.06 to 1.15]	.07	[-.41 to .54]
		TAU	*n=19*	6.79	(2.15)	7.53	(2.22)	7.63	(2.67)				
	LOCF	NFB+TAU	*n*=56	6.36	(1.65)	6.55	(1.66)	6.57	(2.04)	.51	[.12 to .90]	.04	[-.27 to .36]
		TAU	*n*=31	6.61	(1.87)	7.35	(2.20)	7.42	(2.49)				
Longest row	Completers	NFB+TAU	*n=41*	4.76	(0.89)	4.88	(0.90)	4.88	(1.19)	.25	[-.07 to .56]	.13	[-.16 to .43]
		TAU	*n=19*	5.05	(1.08)	5.16	(1.21)	5.16	(1.21)				
	LOCF	NFB+TAU	*n*=56	4.63	(0.91)	4.70	(0.95)	4.70	(1.16)	.21	[-.02 to .44]	.08	[-.12 to .28]
		TAU	*n*=31	4.94	(0.96)	5.13	(1.23)	5.29	(1.30)				
Stroop[F]													
Color/word	Completers	NFB+TAU	*n=39*	100.41	(22.98)	92.85	(21.10)	95.15	(29.68)	-7.44	[-14.05 to -.84]	-2.11	[-8.49 to 4.27]
		TAU	*n=19*	102.32	(28.91)	99.21	(36.62)	92.68	(19.55)				
	LOCF	NFB+TAU	*n*=56	100.55	(24.10)	94.50	(23.05)	96.46	(29.17)	-5.88	[-10.28 to -1.49]	-1.01	[-5.18 to 3.15]
		TAU	*n*=31	97.74	(27.73)	94.06	(32.93)	90.06	(21.83)				
Interference	Completers	NFB+TAU	*n=39*	34.46	(14.63)	30.74	(13.29)	33.28	(21.48)	-3.67	[-9.71 to 2.38]	.48	[-5.37 to 6.33]
		TAU	*n=19*	36.84	(20.22)	32.26	(22.86)	30.68	(13.23)				
	LOCF	NFB+TAU	*n*=56	35.48	(16.09)	32.02	(15.34)	34.20	(21.12)	-3.06	[-7.13 to 1.00]	.61	[-3.20 to 4.42]
		TAU	*n*=31	33.71	(17.59)	29.84	(18.96)	28.87	(12.11)				

Test				Pre-Intervention (T1)		Post-Intervention (T2)		One-Year Follow-Up (T3)		Adjusted Difference T3-T1[C]		Adjusted Difference T3-T2[C]	
	ITT[B]		*n*	*Mean*	*(SD)*	*Mean*	*(SD)*	*Mean*	*(SD)*	*AD*	*[95%CI]*	*AD*	*[95%CI]*
TOL[G]													
Correct score	Completers	NFB+TAU	*n=41*	3.51	(1.83)	3.44	(1.85)	3.59	(2.23)	.20	[-.50 to .91]	.16	[-.41 to .73]
		TAU	*n=18*	3.67	(1.72)	3.83	(2.07)	4.00	(2.50)				
	LOCF	NFB+TAU	*n*=56	3.61	(1.99)	3.41	(2.08)	3.52	(2.34)	.31	[-.19 to .81]	.13	[-.24 to .50]
		TAU	*n*=31	3.71	(1.62)	4.26	(2.03)	4.42	(2.35)				
Move score	Completers	NFB+TAU	*n=41*	31.90	(16.48)	29.83	(15.19)	31.02	(18.91)	-4.13	[-9.52 to 1.26]	-3.18	[-8.01 to 1.65]
		TAU	*n=18*	31.89	(15.51)	32.06	(15.95)	24.50	(12.31)				
	LOCF	NFB+TAU	*n*=56	31.68	(15.50)	31.61	(15.80)	32.48	(18.41)	-3.55	[-7.41 to .32]	-1.72	[-4.88 to 1.43]
		TAU	*n*=31	31.90	(14.94)	28.32	(16.26)	24.00	(13.60)				
Initiation time	Completers	NFB+TAU	*n=41*	20.49	(10.67)	20.39	(19.04)	24.68	(15.25)	5.74	[1.33 to 10.14]	4.62	[-.05 to 9.29]
		TAU	*n=18*	19.50	(10.37)	21.83	(13.73)	26.78	(24.35)				
	LOCF	NFB+TAU	*n*=56	26.43	(21.92)	25.86	(25.12)	29.00	(22.48)	3.33	[.23 to 6.44]	2.59	[-.53 to 5.71]
		TAU	*n*=31	25.94	(22.94)	28.00	(23.21)	30.03	(26.65)				
Execution Time	Completers	NFB+TAU	*n=41*	175.78	(70.92)	142.49	(40.20)	143.10	(55.32)	-36.62	[-56.11 to -17.13]	-12.81	[-30.12 to 4.51]
		TAU	*n=18*	173.11	(49.61)	158.78	(47.79)	132.56	(33.17)				
	LOCF	NFB+TAU	*n*=56	178.68	(69.21)	154.68	(48.83)	155.13	(58.51)	-28.10	[-41.68 to -14.62]	-7.16	[-18.46 to 4.13]
		TAU	*n*=31	177.00	(58.89)	159.13	(61.65)	144.35	(57.32)				
Total Time	Completers	NFB+TAU	*n=41*	196.27	(75.97)	162.88	(44.11)	167.78	(60.55)	-30.88	[-51.78 to -9.99]	-8.19	[-26.99 to 10.61]
		TAU	*n=18*	192.61	(50.43)	180.61	(48.23)	159.33	(39.71)				
	LOCF	NFB+TAU	*n*=56	205.11	(76.34)	180.54	(57.05)	184.13	(66.20)	-24.77	[-39.00 to -10.53]	-4.58	[-16.76 to 7.61]
		TAU	*n*=31	202.94	(66.11)	187.13	(68.94)	174.39	(67.98)				

Note: [A] Data are means (SD), [B] Intention to treat (ITT), [C] Adjusted difference (AD) and 95% confidence interval [95%CI] of one-year follow-up minus pre-intervention are displayed for the total group (NFB+TAU and TAU), [D] d2 attention test, [E] DSB=Digit Span Backwards; [F] Stroop is measured in time in seconds; [G] TOL=Tower of London

Neurocognitive measures

Neurocognitive measures are summarized in Table 3. There were no significant interactions between treatment group and time on the neurocognitive measures. Time interacted with the d2 attention test measures: TN (p<.001), and C (p<.001), reflecting an increase in both scores from pre-intervention to one-year follow-up (see Table 3). There were also interactions with time for some TOL measures: initiation time (p=.040), execution time (p=.002) and total time (p=.014). At the one-year follow-up adolescents took longer to make their first move, but needed less time to execute the task and less time overall to complete the task than pre-intervention (see Table 3).

Post-hoc analyses for stimulant medication use and diagnostic group

LOCF: Post hoc analysis based on LOCF, to control for potential outcome bias due to drop-out, showed behavioral and neurocognitive outcomes comparable to the completion analyses with a decrease of behavioral problems and faster performance of neurocognitive task over time for all adolescents (N=87), irrespective of treatment group (NFB+TAU or TAU). There are four exceptions: 1) in contrast to the completion analyses, the decrease for the YSR attention problem scale did not follow a significant different time course in the NFB+TAU and TAU groups (p=.080). 2) There was no longer a significant effect over time for the TOL initiation time (p=.105). Conversely, time effects became significant for 3) the DSB with an increase in total score (p=.020) and 4) the Stroop color/word card with a decrease in execution time (p=.013).

Stimulant medication use: The ADHD HI scale, MINI, YSR and neurocognitive measures showed no interactions with time for either treatment group or stimulant medication use. There was an interaction between time, treatment group and stimulant medication use for the ADHD inattention scale (p=.011). There was a reduction in inattention problems from pre-intervention, M=4.23, SD=2.42 to follow-up, M=2.83, SD=2.31, $AD_{T3\text{-}T1}$=-1.55, 95%CI=[-2.25 to -.85], for stimulant-medicated adolescents irrespective of whether they received neurofeedback. Separate analyses for each treatment group showed that stimulant-free adolescents in the NFB+TAU group showed a reduction in inattention from pre-intervention, M=5.36, SD=2.08 to one-year follow-up, M=2.68, SD=2.38, $AD_{T3\text{-}T1}$=-2.68, 95%CI=[-.3.73 to -1.64]; however stimulant-free adolescents in the TAU group reported similar levels of inattention at pre-intervention, M=6.00, SD=1.93, and one-year follow-up, M=5.63, SD=2.77, $AD_{T3\text{-}T1}$=-.38, 95%CI=[-2.04 to 1.29].

ADHD or ASD+ADHD: Post-hoc analysis showed no interactions between time, treatment group and diagnostic group on attention or neurocognitive measures.

DISCUSSION

Long-term effects on behavioral and neurocognitive functioning from supplementing TAU with neurofeedback were investigated in the present study, using a multicenter parallel RCT design. This is the first study to investigate the long-term additional value of using neurofeedback to supplement TAU up to one year after the end of the intervention. Overall, the adolescents reported reductions in ADHD-symptoms, irrespective of whether they had received neurofeedback. Neurocognitive measures of attention or processing speed showed improvements between pre-intervention and follow-up indexed by decreased execution time on the TOL task and an increase in total processed items on the d2 attention test. There was no additional benefit from supplementing TAU with neurofeedback one year after treatment. This is consistent with a naturalistic six-month follow-up study in which similar improvements were found in stimulant-medicated children and children who had received neurofeedback (Meisel et al., 2013). However, it should be noted that by the time of the follow-up, eight of the twelve children who had received neurofeedback had started stimulant medication treatment (Meisel et al., 2013). Our findings are also consistent with the randomized studies, which showed that directly after the treatment period neurofeedback was as effective as stimulant medication (Duric et al., 2012; Meisel et al., 2013), or a combination of stimulant medication and neurofeedback (Duric et al., 2012).

One RCT study found long-term positive results for neurofeedback (n=38) compared with computerized attention training (n=23), six months post-treatment in stimulant-free children with ADHD (Gevensleben et al., 2010). In this study children for whom stimulant medication was indicated were excluded from the trial or excluded from the follow-up analysis; this probably excluded children with more severe ADHD symptoms. In consequence the effectiveness of neurofeedback as a treatment for ADHD in this study cannot be generalized to children with more severe ADHD symptoms. A recent published RCT did overcome this generalization problem by including children while standard community care continued: a larger decrease of ADHD problems was found from pre-intervention to six month follow-up for children receiving neurofeedback (n=34) than children receiving only standard community care (n=36) (Steiner et al., 2014). However, significant results were only found on parent-reports and as such bias of the parents for the intervention might have influenced the outcomes of the non-blinded study. By investigating the effects of neurofeedback as an additional treatment for adolescents with ADHD with a combination of behavioral and neurocognitive measures, we aimed to ensure the ecological validity of the current study. Nevertheless, this also resulted in several limitations. For example, the target population consists of a heterogeneous group of male adolescents with complex problems and there was variety in the prescription of stimulant medication.

Dropout during the course of the study did not seem to have influenced the outcomes. The effects of stimulant medication use and comorbid ASD and possible interactions with the effects of the treatment over time were also explored in the current study. Adolescents with comorbid ASD did

not respond to the interventions differently from adolescents with ADHD only. Stimulant-medication use at one-year follow-up interacted with treatment group on inattention assessed by the ADHD inattention subscale: inattention did not decrease in stimulant-free adolescents who received TAU without neurofeedback; however stimulant-free adolescents receiving TAU did report reduced attention problems on the MINI inattention scale and the YSR attention problems scale. The small TAU sample (n=19; stimulant-free *n*=8, stimulant-medicated *n*=11) was a limitation in this subgroup analysis and precludes strong conclusions.

In conclusion, one year after treatment the reduction in ADHD symptoms and improvements in neurocognitive performance were similar in adolescents who received neurofeedback in addition to TAU and adolescents receiving TAU; these results do not support the use of theta/SMR neurofeedback as a supplement to TAU to produce enduring improvements in behavior or neurocognitive functioning in adolescents with ADHD. The absence in the current study of long-term effects of neurofeedback additional to those of stimulant medication, combined with the absence of specific effects of neurofeedback over sham neurofeedback (24-27) and the requirement for lengthy training (20 to 40 sessions) (18), do not support use of theta/SMR neurofeedback as a treatment for adolescents with ADHD in clinical practice.

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CHAPTER 8

Summary and Discussion

The morbid alterations to which attention is subject, may all be reduced under the two following heads:

First. The incapacity of attending with a necessary degree of constancy to any one object.
Second. A total suspension of its effects on the brain.

"The incapacity with a necessary degree of constancy to any one object, almost always arises from an unnatural or morbid sensibility of the nerves, by which means this faculty is incessantly withdrawn from one impression to another." (….) "When born within a person it becomes evident at a very early period of life, and has a very bad effect, inasmuch as it renders him incapable of attending with constancy to any one object of education"
A. Crichton (2008)

INTRODUCTION

The first aim of this thesis was to explore psychophysiology in adolescents with ADHD and combined ASD+ADHD as well as possible clinical implications (Part 1). The second aim of this thesis was to investigate whether neurofeedback has additional value to treatment as usual in improving behavior and neurocognitive functioning in adolescents with ADHD (Part 2). The current chapter summarizes the main findings and discusses limitations, future research and clinical implications.

SUMMARY

Part 1: Psychophysiology in adolescents with ADHD and comorbid ASD+ADHD

Attention deficit/hyperactivity disorder has a worldwide prevalence of around 5% (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007; Willcutt, 2012) and as such constitutes the most common neurodevelopmental disorder. In addition, a large number of youngsters with autism spectrum disorders (ASD) display comorbid attention deficit/hyperactivity disorder (ADHD) symptoms. Physiological measures, such as cardiac reactivity, electroencephalogram (EEG) power spectra and event related potentials (ERPs) have been related to ADHD symptomatology. The first part of the thesis explored overlap and differences in psychophysiological correlates of ADHD between adolescents with ADHD and adolescents with comorbid ASD and ADHD (ASD+ADHD), on and off stimulant medication.

In **Chapter 2**, overlap and differences in cardiac activity between adolescents with ADHD and adolescents with combined ASD+ADHD were explored. Atypical cardiac activity such as increased parasympathetic activation with lower heart rate (Negrao, Bipath, van der Westhuizen, & Viljoen, 2011) and increased heart rate variability (Borger & van der Meere, 2000; Borger et al., 1999; Negrao et al., 2011) have been related to ADHD. In contrast, ASD has been associated with increased sympathetic activation (Bal et al., 2010; Daluwatte et al., 2012; Van Hecke et al., 2009). Accordingly, it was expected that the adolescents with ASD+ADHD would show signs of more sympathetic and less parasympathetic activation than ADHD adolescents. However, when comparing cardiac measures in a clinical sample, adolescents diagnosed with ADHD (n=36) and ASD+ADHD (n=20) showed similar cardiac reactivity. Stimulant-medicated adolescents (n=31) showed decreased adaptation of LF/HF ratio and faster reaction times than stimulant-free adolescents (n=25), irrespective of diagnosis. In conclusion, this study underlines overlap in cardiac activity between adolescents with ADHD and combined ASD+ADHD.

Chapter 3 aimed to explore overlap and differences in theta and beta power spectra between adolescents with ADHD versus combined ASD+ADHD. In contrast to the overlap in cardiac activity demonstrated in chapter 2, EEG power spectra differed in adolescents with ADHD (n=33) versus adolescents with combined ASD+ADHD (n=20). Adolescents with ADHD displayed more absolute theta activity than adolescents with combined ASD+ADHD during the eyes open and task conditions,

irrespective of stimulant medication use. During eyes closed absolute theta was similar for both diagnoses. In addition, adolescents with ADHD but not adolescents with ASD+ADHD showed an association between diminished attention test performance and increased theta in the eyes open condition. Indeed, increased theta power during resting state conditions (Cortese, 2012; Loo & Makeig, 2012; Snyder & Hall, 2006), mainly in frontocentral regions (Loo & Makeig, 2012), is one of the most robust findings in ADHD. Consequently, the results of Chapter 3 indicate that adolescents with ASD+ADHD exhibited fewer of the physiological signs in the EEG usually associated with ADHD, although there was an overlap in attention problems between the adolescents with ADHD en ASD+ADHD.

Chapter 4 explored event related potentials during an auditory oddball task. Psychophysiological measures of brain functioning, such as ERP indices, are related to cognitive functions such as attention, response selection, inhibition, and response monitoring (Johnstone, Barry, & Clarke, 2013). ERP components differed dependent on diagnoses and stimulant medication use. In combined ASD+ADHD (n=20), the N2 peak amplitude and difference wave was smaller in stimulant-free (n=9) than in stimulant-medicated adolescents (n=11), but in adolescents diagnosed with ADHD there was no such difference between stimulant-free (n=14) and stimulant-medicated (n=19) participants. The smaller N2 difference wave suggests that stimulant-free adolescents with ASD+ADHD might have more problems to discriminate between standard and target stimuli than stimulant-medicated adolescents with combined ASD+ADHD. In addition, medication use was associated with reduced N1 peak latencies in ADHD adolescents and with prolonged N1 peak latencies in ASD+ADHD. Chapter 4 indicates distinctive ERP activity in stimulant-medicated and stimulant-free adolescents that dependents on diagnostic group.

In sum, results from the first part of this thesis show that whereas there is behavioral overlap and overlap in cardiac activity between adolescents with ADHD and adolescents with combined ASD+ADHD, there are differences in brain activity between these diagnostic subgroups. Such differences are of importance, because this may indicate that treatments developed for ADHD work out in a different manner in adolescents with ASD+ADHD compared to adolescents with ADHD.

Part 2: The additional value of neurofeedback over treatment as usual

Neurofeedback is seen as a potentially effective treatment to reduce Attention Deficit Hyperactivity Disorder (ADHD)-symptomatology, mainly attention problems. Neurofeedback intends to alter brain activity by giving feedback of electroencephalogram (EEG) activity to patients and subsequently improve behavior using operant conditioning principles. Overall, youngsters with ADHD show increased theta (Cortese, 2012; Loo & Makeig, 2012; Snyder & Hall, 2006), and decreased beta (Cortese, 2012; Snyder & Hall, 2006) activity compared to typical developing youngsters. Accordingly, the most frequently used neurofeedback protocol is the theta/beta training, which aims to decrease theta (4-7Hz) and increase SMR (12-15Hz) or beta (12-20Hz) activity (Lofthouse, Arnold, Hersch,

Hurt, & DeBeus, 2012; Loo & Makeig, 2012; Moriyama et al., 2012). Typically, the complete neurofeedback intervention comprises 20 to 40 training sessions (Loo & Makeig, 2012). In the second part of the thesis additional effects of neurofeedback over treatment as usual on behavioral and neurocognitive functioning were investigated.

Using a multicenter parallel-randomized controlled trial design, 90 male adolescents with a DSM-IV-TR diagnosis of ADHD were randomized to receive either a combination of neurofeedback and treatment as usual or only treatment as usual. Neurofeedback treatment consisted of approximately 37 sessions of theta/SMR-training on the vertex (Cz). The duration of the intervention period was around 25 weeks. In total, 71 adolescents (mean age 16.1 years, standard deviation 3.3 years) were compared on behavioral and neurocognitive measures pre-intervention and immediately post-intervention. One-year after the intervention period, 60 adolescents were compared again on behavioral and neurocognitive measures.

In **Chapter 5** the additional effects of neurofeedback over treatment as usual on behavior were investigated direct after the intervention period. For all adolescents with ADHD, self-reported and parent reported behavioral problems such as inattention and hyperactivity/impulsivity decreased from pre-intervention to post-intervention. There was no difference in this decrease between the 45 adolescents who had received neurofeedback in addition to treatment as usual and the 26 adolescents who had received only treatment as usual. Furthermore, stimulant-medication use or the presence of comorbid ASD had no effect on the reported decrease in behavioral problems over time. Similarly, reported side-effects were comparable regardless of received treatment. However, the stimulant-free adolescents reported a decrease in headache frequency after the intervention period, whereas the stimulant-medicated adolescents did not report such a decrease. In conclusion, on behavioral outcomes, neurofeedback in combination with treatment as usual was equally effective compared to only treatment as usual. There were no additional behavioral effects of neurofeedback as such.

After investigation of the behavioral effects, in **Chapter 6** potential additional effects of neurofeedback on neurocognitive functioning were examined. Before and immediately after the intervention period, all participants were compared on several neurocognitive measures: the d2 test of attention, the digit span backwards, the Stroop test and the Tower of London. Results showed an improvement in neurocognitive measures of attention at post-intervention for all participants. They needed less time to process information, while accuracy remained unchanged. Working memory and planning indices remained stable over time. The 45 adolescents who received neurofeedback in addition to treatment as usual did not outperform the 26 adolescents who did not receive neurofeedback. Similar to chapter 5, no additional value of neurofeedback over treatment as usual was found. Accordingly, this study did not provide evidence for using theta/SMR neurofeedback to enhance neurocognitive performance as additional intervention to TAU for adolescents with ADHD symptoms.

A year after the intervention period, 60 adolescents were assessed again. In **Chapter 7,** long-term additional value of neurofeedback to treatment as usual on ADHD symptom reduction was

investigated. For this purpose, behavioral self-reports, neurocognitive measures and side effects were compared between 41 adolescents who had received neurofeedback as additional treatment and 19 adolescents who had received only treatment as usual. The adolescents reported a decrease in behavioral problems from pre-intervention through one-year follow-up. Furthermore, the adolescents became faster in performing the neurocognitive tasks, irrespective of received treatment. Headaches decreased over time and reported sleep problems stayed the same over time. Similar to chapter 5 and chapter 6, neurofeedback in combination with treatment as usual was equally effective compared to only treatment as usual for adolescents with ADHD.

To conclude, the second part of this thesis investigated the additional effects of neurofeedback to treatment as usual. No additional direct or long-term effects of neurofeedback over treatment as usual were found with respect to behavior or neurocognitive functioning in adolescents with ADHD. Considering the absence of robust additional direct or long-term effects, the results do not support the use of theta/SMR neurofeedback as additional treatment to enduringly improve behavior or enhance neurocognitive functioning in adolescents with ADHD and comorbid disorders in clinical practice.

DISCUSSION

In the 18th century Sir Alexander Crichton was the first to describe a disorder similar to ADHD with "morbid alternations of which attention is subject" in his second book: An inquiry into the nature and origin of mental derangement: comprehending a concise system of the physiology and pathology of the human mind (Crichton, 1798). Sir Crichton already combined physiology and pathology by stating that these morbid alternations can be seen as "The incapacity of attending with a necessary degree of constancy to any one object" and "A total suspension of its effects on the brain." Ironically, the first published edition of his chapter underlines that alternations in attention are not always morbid, being even present during his own study, by stating that: "The morbid alterations to which attention is subject, may all be reduced under the three following heads" (see Chapter 1). Only two heads followed after this description. Over time, this possible alternation in attention was corrected: in later published versions the "three heads" (Crichton, 1798) became "two heads" (Crichton, 2008). Correction of alternations in attention, however, is not that simple in ADHD. By combining physiology and behavior, this thesis aimed to look more closely at ADHD symptomatology and related physiology (part 1) and subsequently whether it is possible to train brain functioning enduringly to improve behavior and cognition with neurofeedback in ADHD patients (part 2).

Two of a kind: ADHD and ASD+ADHD

The first part of this thesis indicates that whereas there is behavioral overlap and overlap in cardiac activity between adolescents with ADHD and adolescents with combined ASD+ADHD, there are differences in brain activity. These differences are of importance, because this may indicate that treatments developed for ADHD work differently in adolescents with ASD+ADHD compared to adolescents with ADHD.

The assumption for the cardiac reactivity was that ADHD is associated with signs of increased parasympathetic activation, whereas ASD is associated with signs of increased sympathetic activation. Accordingly, it was expected that adolescents with ASD+ADHD would show signs of more sympathetic and less parasympathetic activation than ADHD adolescents. However, cardiac activity and task-related cardiac adaptation were similar for the adolescents with ASD+ADHD and the adolescents with ADHD. A possible rational for these findings is that there are psychophysiological constructs related to the ADHD symptomatology, responsible for the overlap in cardiac activity between ADHD and ASD+ADHD.

Interestingly, regarding brain functioning, there was some overlap between ADHD and ASD+ADHD adolescent, but some differences emerged as well. The most prominent finding was that adolescents with ADHD had increased levels of theta activity, with their eyes open and while performing a task compared to adolescents with combined ASD+ADHD. Furthermore, for adolescents with ADHD, theta in resting condition with eyes open was negatively related to attention task performance. In contrast, adolescents with combined ASD+ADHD did not show this relation.

Elevated theta activity is one of the most robust finding in ADHD (Cortese, 2012; Loo & Makeig, 2012; Snyder & Hall, 2006). Considering theta (4-7 Hz) has been negatively related to vigilance (Banaschewski & Brandeis, 2007), this may indicate that elevated theta and decreased vigilance are better explanations for attentional problems in adolescents with ADHD than in adolescents with ASD+ADHD. The results suggest that attentional problems in ASD+ADHD may result from other brain dysfunctions, such as abnormal neuronal connectivity (Billeci et al., 2013; Coben, Clarke, Hudspeth, & Barry, 2008) and top-down processing problems (Gomot & Wicker, 2012), rather than from frontocentral underarousal per se. The ERP outcomes point in a similar way to processing problems in ASD. Stimulant-free adolescents with ASD+ADHD had a smaller N2 to target stimuli, than stimulant-medicated adolescents with ASD+ADHD. There was no such difference between stimulant-free and stimulant-medicated adolescents with ADHD. The smaller N2 to target stimuli hints that the stimulant-free adolescents with combined ASD and ADHD have more problems with stimuli discrimination.

It was expected that stimulant medication partly 'normalizes' psychophysiology in ADHD. Consequently, the expectation was that the stimulant-medicated adolescents would show less neurocognitive and physiological signs usually associated with ADHD than the stimulant-free adolescents. Indeed, stimulant-medicated adolescents showed faster reaction times and reaction time was less variable than in stimulant-free adolescents, irrespective of diagnosis. In addition, stimulant-medicated adolescents showed in the cardiac measures a higher LF/HF ratio in resting condition compared to stimulant-free adolescents. The LF/HF ratio during performance of an auditory oddball task however did not differ in respect to stimulant use. Accordingly, adaptation of LF/HF ratio, that is the increase of LF/HF ratio typically seen from rest condition to task condition, was decreased. Whereas decreased parasympathetic activation is generally viewed as a shift to normalization, a decrease in autonomic modulation could be less favorable. It remains unclear what the implications are for everyday life when stimulant-medicated youngsters are less able to shift physiologically between rest conditions and demanding cognitive activities.

It is remarkable that stimulant-medicated and stimulant-free adolescents did not differ in the amount of theta or beta activity. Decreased theta and increased beta after stimulant medication use is typically seen in youngsters with ADHD after stimulant medication use (Clarke, Barry, Bond, McCarthy, & Selikowitz, 2002; Clarke et al., 2003; Hermens et al., 2005; Loo & Barkley, 2005). However, although stimulant medication partly normalizes theta and beta power, children with ADHD do not reach similar theta and beta levels as TD children (Clarke et al., 2002; Clarke et al., 2003). Baseline differences in age between adolescents on and off stimulant medication in our sample may have contributed to the lack of effects of stimulant medication: the stimulant-free adolescents were, on average, older than stimulant-medicated adolescents. Since aging (Segalowitz, Santesso, & Jetha, 2010) as well as using stimulant medication (Clarke et al., 2002; Clarke et al., 2003; Hermens et al., 2005; Loo & Barkley, 2005) results in decreased theta power, the two effects may have cancelled each other out. In line with the review by Segalowitz et al. (2010) the current study found a clear maturation effect,

with older adolescents displaying lower absolute power across all frequency bands, particularly in the posterior region, and increased relative beta.

Similarly, stimulant medication appears to regulate ERP activity, with increased N2 (Pliszka et al., 2007) and P3 (Groom et al., 2010; Hermens et al., 2005) amplitudes after stimulant medication use in adolescents with ADHD. In line with these outcomes, we found a larger N2 amplitude in stimulant-medicated than in stimulant-free adolescents with combined ASD+ADHD. Surprisingly, there was no such difference for stimulant medication use in adolescents with ADHD. Furthermore, like the study of Groen et al. (2008), we did not find larger P3 amplitudes for stimulant-medicated compared to stimulant-free adolescents. Note that whereas the studies that found differences in P3 amplitude looked at youngsters with ADHD on and off stimulant medication in a within subject design (Groom et al., 2010; Hermens et al., 2005), whereas our study and the study of Groen et al. (2008) analyzed differences between subjects. By controlling for individual differences with a within subject design differences of stimulant medication use might be better demonstrable than differences between two separate patient groups. For the peak latencies we did find differences between stimulant-medicated and stimulant-free adolescents dependent on the kind of diagnosis. The N1 peak latency was longer in stimulant-medicated adolescents compared to stimulant-free adolescents with combined ASD+ADHD. An opposite pattern was observed for the adolescents with ADHD, where N1 peak latency was shorter in stimulant-medicated than in stimulant-free adolescents. Shorter latencies are generally seen as an indication of more efficient information processing. Nonetheless, the results also showed that prolonged central N1 latency was associated with larger N1 amplitudes. In addition, long N1 latency was related with less reaction time variability in adolescents with combined ASD+ADHD. These results suggest that the later N1 peak is related with a more consistent reaction to target stimuli, especially for adolescents with combined ASD+ADHD.

The studies in the first part of this thesis demonstrated differences between adolescents with ADHD and combined ASD+ADHD. The differences were found in a clinical sample of adolescents recruited with clinical DSM-IV ADHD symptoms. Stimulant medication use was allowed and continued on the assessment days. Accordingly, the sample resembles clinical practice but is also heterogeneous in nature with respect to diagnosis (ADHD or combined ASD+ADHD), stimulant medication use and age. Further systematic research on the psychophysiological aspects of ADHD and ASD+ADHD and their implications is therefore warranted. Replication of these psychophysiological results with a larger sample size are needed in a randomized controlled trial, ideally with a controlled stimulant medication titration trial including physiological baseline measures with stimulant-free adolescents with ADHD, ASD+ADHD, ASD. Such a titration trial would control for the baseline differences in stimulant medication use and age that were observed in the current study. Adolescents continued stimulant medication on the day of assessment as described by their physician. Accordingly, initial differences in stimulant medication use could not be controlled for. In addition, the stimulant-medicated adolescents in this study were on average younger than the stimulant-free adolescents. Although we controlled for age statistically, it is possible that stimulant medication use and maturation

may affect psychophysiological measures similarly. Furthermore, the diagnostic assignments in this study were based on clinician's decisions using DSM-IV (American Psychiatric Association, 2000) criteria; whilst this increased the ecological validity of the study, information about specific diagnostic aspects of ASD were not available. Including diagnostic interviews such as the Autism Diagnostic Interview (Lord, Rutter, & Le Couteur, 1994) or the Autism Diagnostic Observation Schedule (Lord et al., 1989) in future research, could give more detailed information about specific characteristics of ASD. Moreover, inclusion of a control group of typically developing adolescents would make it possible to determine whether psychophysiological patterns in the diagnostic groups differ from those of TD adolescents.

In conclusion, whereas behavioral and autonomic physiological measures seem to overlap between adolescents with ADHD and combined ASD+ADHD, the results described in the first part of this thesis indicate that there might be differences in underlying brain mechanisms related to ADHD symptomatology. Clinical implications of these physiological differences in reaction to stimulant medication use should be further investigated in larger groups of participants and more strict research designs to provide targets for optimizing treatment of ADHD in ASD.

Neurofeedback: ingredients of effectiveness

In the second part of the thesis we investigated the additional value of neurofeedback to treatment as usual to reduce ADHD symptoms and enhance neurocognitive functioning for adolescents with ADHD and comorbid disorders. No additional direct or long-term effects of neurofeedback over treatment as usual were found to improve behavior or neurocognitive functioning in adolescents with ADHD. Accordingly, we concluded that the results do not support implementation of theta/SMR neurofeedback as additional treatment to enduringly improve behavior or enhance neurocognitive functioning for adolescents with ADHD and comorbid disorders in clinical practice.

A meta-analysis concluded in 2009 that neurofeedback for the treatment of ADHD "efficacious and specific" is (Arns, de Ridder, Strehl, Breteler, & Coenen, 2009). The estimated effect sizes vary between medium for hyperactivity and large for inattention and impulsivity reduction (Arns et al., 2009). In the years thereafter, this non-pharmacological intervention for ADHD received increasing interest. This resulted in several reviews in 2012, indicating that neurofeedback is a "probably effective" treatment for ADHD (Gevensleben, Rothenberger, Moll, & Heinrich, 2012; Lofthouse et al., 2012; Moriyama et al., 2012). Another review was less positive with regard to theta/beta neurofeedback, stating that "The state of the published, peer reviewed literature on theta/beta training, as it currently stands, does not support theta/beta training even as an adjunct treatment" (Loo & Makeig, 2012). A new meta-analysis in 2013 showed that effectiveness of neurofeedback in improving behavior in ADHD decreased to non-significant levels in the case of probably blinded assessment (Sonuga-Barke et al., 2013). Similarly, results of a systematic review did not support the effectiveness of neurofeedback in improving neurocognitive functioning in ADHD

(Vollebregt, van Dongen-Boomsma, Buitelaar, & Slaats-Willemse, 2013). Consequently, effectiveness estimations of neurofeedback thus far range from "efficacious and specific" to not effective.

Considering the wide range of effectiveness estimations within the last four years, it is important to ask how these differences originated. Studies into the effectiveness of neurofeedback for the treatment of ADHD have been hampered by many methodological problems. Not only with regard to the designs of the studies that vary greatly, but also with regard to the proposed neurofeedback training protocol. To narrow the focus of the current discussion, only studies that applied frequency -mainly theta/beta- training protocols to improve functioning in patients with ADHD are discussed in more detail.

The first non-randomized studies (e.g. Fuchs, Birbaumer, Lutzenberger, Gruzelier, & Kaiser, 2003; Monastra, Monastra, & George, 2002) all showed positive effects for neurofeedback. However, these non-randomized studies could not control for non-specific effects. For example, parents with a preference for an intensive non-pharmacological treatment like neurofeedback, might also be more likely to encourage changes of the child with ADHD in daily life. Typical neurofeedback training consists of 20 to 40 sessions. Those parents able to bring their child to the therapy for an extended period of time, multiple times a week, might overall be better able to give their child a more structured and predictable surrounding. In addition, the amount of time invested in the treatment by the child, therapist and parents, might make parents more inclined to see and report positive changes in the behavior of their child. Besides various non-specific effects of parent-informed behavioral assessment, maturation and practice effects are likely to result in improved performance on neurocognitive tests in children.

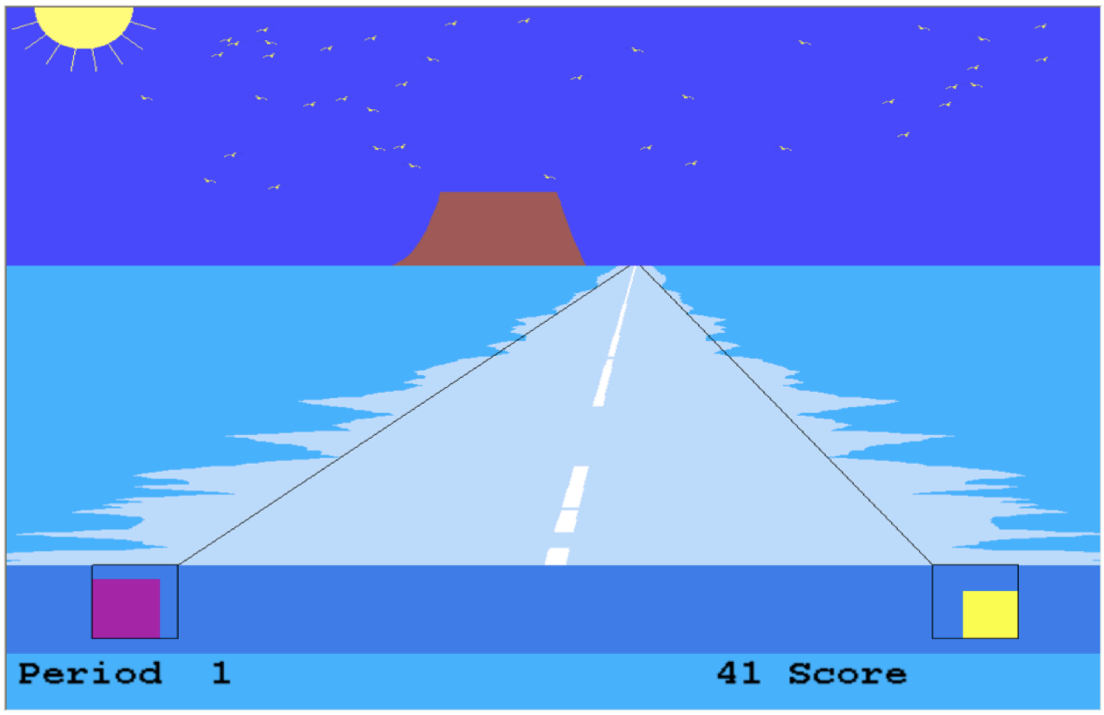
To control for non-specific investment and preference effects, studies with a randomized controlled trial (RCT) design were implemented. Parents were no longer able to choose a treatment of their preference, as in the aforementioned studies. Rather, parents and children could choose to participate in a study, after which they were randomized to a specific treatment. In one of the first large RCT studies, randomized stimulant-free children received either neurofeedback (n=59) or computerized attention training (n=35) (Gevensleben, Holl, Albrecht, Vogel, et al., 2009). The children received an equal number of training sessions irrespective of treatment allocation. Accordingly, the study simultaneously prevented a bias resulting of investment and/or preferences of the parents. Furthermore, the children receiving neurofeedback improved more in behavior as reported by parents and teacher than the children receiving computerized attention training (Gevensleben, Holl, Albrecht, Vogel, et al., 2009). Six-months post-treatment, parents still reported better behavior for the children who had received neurofeedback than the children who had received the attention training (Gevensleben et al., 2010). Unfortunately, only 70% of the teacher reports was received at follow-up and therefore not analyzed (Gevensleben et al., 2010). A limitation for extrapolating these results to clinical practice is that it is only applicable to stimulant-free children (Gevensleben et al., 2010; Gevensleben, Holl, Albrecht, Vogel, et al., 2009). In case stimulant medication use was indicated, children were excluded from trial participation or follow-up analysis. In this way the study introduced a

selection bias by excluding children with probably more severe ADHD at the start of the study, and at post-treatment, excluding children for whom ADHD symptoms became more severe.

Other RCT studies tried to overcome this problem of generalizability by comparing neurofeedback with stimulant medication use in children with ADHD. The largest of these studies showed similar improvements in attention as reported by parents for neurofeedback (*n*=30), stimulant medication (*n*=31) or combined neurofeedback and stimulant medication (*n*=30) (Duric, Assmus, Gundersen, & Elgen, 2012). Comparable, a smaller study with an RCT design also showed similar improvements in attention for neurofeedback (*n*=12) and stimulant medication (*n*=11) (Meisel, Servera, Garcia-Banda, Cardo, & Moreno, 2013). In contrast, there is another study showing improvement in behavior in stimulant-medicated youngsters (*n*=15), but not in those receiving neurofeedback (*n*=14). Although these three studies look similar in study design, a major difference includes the applied medication protocol. The two studies that show comparable improvements for neurofeedback and stimulant medications use, applied medication titration with the daily dosage depending on weight, with 1 mg per kg (Duric et al., 2012; Meisel et al., 2013). In contrast, the study that found stimulant medication to be superior to neurofeedback, individualized medication use by incorporating a double-blind placebo controlled medication trial (Ogrim & Hestad, 2013). Titrating stimulant medication based on body weight is applied often in research. However, several studies criticize this way of stimulant titration in ADHD (Greenhill et al., 2002; Rapport & Denney, 1997). Accordingly, it might be that stimulant medication did not reach an optimal effect in the first two studies. Further research, comparing neurofeedback with stimulant medication, titrated with a stepwise double blind placebo controlled protocol is essential to see if neurofeedback is able to serve as an alternative for stimulant medication.

To date, double-blinded studies fail to find additional value of neurofeedback over sham-neurofeedback on behavioral outcomes in children with ADHD (Arnold et al., 2013; Perreau-Linck, Lessard, Levesque, & Beauregard, 2010; van Dongen-Boomsma, Vollebregt, Slaats-Willemse, & Buitelaar, 2013). In addition, none of the double-blinded studies found additional improvements on neurocognitive measures for neurofeedback over sham-neurofeedback in children with ADHD (Arnold et al., 2013; Vollebregt et al., 2013) and healthy students with ADHD features (Logemann, Lansbergen, Van Os, Bocker, & Kenemans, 2010). The results of these blinded studies underline that effects found in non-blinded studies might also resemble non-specific effects, instead of specific effects of neurofeedback.

***Figure 1**: Graphics as presented to the adolescent for visual feedback*



Note: graphics of neurofeedback training with 'EEGer' neurofeedback software version 4.2.1 (EEGer Spectrum Systems)

Neurofeedback protocols used in RCT studies have been debated. For example, it is hypothesized that automatic thresholds might be less effective than manual adapted threshold (Lansbergen, van Dongen-Boomsma, Buitelaar, & Slaats-Willemse, 2011). Nevertheless, comparing neurofeedback with automatic versus manual adapted thresholds did not result in differences on behavioral outcomes (van Dongen-Boomsma et al., 2013). Furthermore, it is assumed that explicit learning strategies are necessary for neurofeedback to be effective (Lansbergen et al., 2011). However, introducing more active learning strategies, did not result in more positive outcomes for neurofeedback in one study (van Dongen-Boomsma et al., 2013). Another consideration is the way in which feedback is provided to the youngsters: movies (i.e. Duric et al., 2012; Ogrim & Hestad, 2013; van Dongen-Boomsma et al., 2013) or complex computer game graphics (i.e. Arnold et al., 2013) might distract from the actual neurofeedback training. Comparing neurofeedback with simple graphics (n=11) to attractive computer games (n=11) did not confirm this theory (Palsson, Pope, Ball, Turner, & Nevin, 2001, March). The current study used simple graphics as feedback (see Figure 1). Despite graphical differences between our study and Duric et al. (2012), which used movies or video games, both studies failed to find evidence for additional value of neurofeedback.

EEG frequency training aims to inhibit or reinforce particular frequency bands. Different protocols have been applied across different studies. The "Lubar" protocol trains to inhibit theta and reinforce SMR or beta activity, in a relaxed but focused state (Lubar, 2003; i.e. the current study). Accordingly, controlling for muscle tension, which is mostly reflected in the higher frequency bands, is important. Other studies trained theta/beta while correcting for eye movements (i.e. Gevensleben,

Holl, Albrecht, Vogel, et al., 2009; note that theta/beta training was comined with training of slow cortical potentials). Finally, some studies used individualized training protocols (i.e. Lansbergen et al., 2011) that mostly amounted to training of theta/SMR (i.e. van Dongen-Boomsma et al., 2013). It might be that effectiveness of neurofeedback depends on the applied training protocol. However, at this moment training protocols are used alternately in clinical practice as well as in research. There is no consensus on the exact kind of protocol to apply for the treatment of ADHD. Therefore, additional knowledge about specific working mechanisms of neurofeedback on the brain is necessary before neurofeedback protocols can be adapted appropriately for the treatment of psychiatric disorders.

Neurofeedback intends to train EEG-activity. Accordingly, it is remarkable that robust changes in EEG-activity have not yet been found. In the study of Gevensleben, Holl, Albrecht, Schlamp, et al. (2009), the authors noted a linear decrease from frontal to parietal in the difference between pre and post theta in the neurofeedback group, whereas the attention training group did not show such an effect. Notwithstanding the changes in patterns of difference scores, the study did not report on significant decreased theta from pre to post training for specific electrode positions. Especially, significant decreased theta at Cz would have been expected since the theta/beta protocol with electrode placement on Cz was applied. In addition, no differences between treatment allocations in beta were found, whereas considering the protocol, increased beta was expected for the children receiving neurofeedback. In contrast, beta decreased over time, mainly frontal, as a function of age and intelligence, irrespective of received treatment. Similarly, another neurofeedback study that looked at post-treatment changes in frequency bands did not demonstrate significant changes compared to the pre-treatment EEG (Kropotov et al., 2007). It can be reasoned that changes in brain activity are of minor importance compared to the aim of neurofeedback to achieve behavioral improvement. However, neurofeedback is based on the assumption that ADHD symptoms originate from under or over activity in specific brain areas. This over or under activity is measured by an EEG recording in resting conditions with eyes open and eyes closed and this recording is used to determine the applicable training protocol. Consequently, it seems reasonable to expect changes in EEG activity after the training. An explanation for the absence of significant EEG changes from pre- to post-treatment is provided by the fact that these EEG recordings take place during resting conditions (Arns et al., 2009; Gevensleben, Holl, Albrecht, Schlamp, et al., 2009). EEG recordings in a resting state seem to contradict with the assumption that neurofeedback intends to train the brain to be more flexible and better able to regulate activation states during task performance. Potentially, changes in brain activation could be most pronounced during task performance. Indeed, during the performance of an attention task, differences were found in event related potentials (Kropotov et al., 2007; Wangler et al., 2011). At this moment, other large RCT studies have not (yet) looked at changes in frequency bands after the intervention period. Therefore, exploring differences within frequency bands between intervention conditions is warranted to determine whether it is possible to train frequency bands in youngsters with ADHD.

Stimulant medication use and comorbidity of ASD did not affect the outcomes in our study. In the first part of this thesis, differences in stimulant medication and diagnoses were described. We saw that during resting with eyes open and during task performance the adolescents with ADHD had significant more theta than the adolescents with combined ASD+ADHD. Elevated theta and decreased beta activity in ADHD (Cortese, 2012; Loo & Makeig, 2012; Snyder & Hall, 2006) is associated with decreased vigilance and decreased attention (Banaschewski & Brandeis, 2007), respectively. Accordingly, neurofeedback protocols aim to decrease theta and increase beta and subsequently improve behavior. Since the adolescents with ASD+ADHD display less theta activity than adolescents with ADHD in the first place, improvements in behavior by decreasing theta activity (if possible) using neurofeedback would probably be less pronounced in adolescents with ASD+ADHD than in adolescents with only ADHD. However, in the current study improvements in cognition and behavior were similar for both diagnostic groups. Similarly, stimulant-medicated adolescents generally display less theta activity than stimulant-free youngsters with ADHD (Clarke et al., 2002; Clarke et al., 2003; Hermens et al., 2005; Loo & Barkley, 2005) and stimulant medication is effective in reducing ADHD symptoms (Faraone & Buitelaar, 2010; Greenhill et al., 2001) and improving neurocognitive functioning (Coghill et al., 2013) in youngsters with ADHD. Consequently, expected improvements with neurofeedback would be smaller in stimulant-medicated than in stimulant-free adolescents. The current study, however, did not find such differences in improvement for stimulant-medicated and stimulant-free adolescents who had received neurofeedback.

The main question of the second part of this thesis was if neurofeedback has additional value to treatment as usual in reducing ADHD symptoms in adolescents with ADHD and comorbid disorders. The current study found similar improvements in behavior and neurocognitive functioning direct after the intervention period and at one-year follow-up, irrespective of received treatment. The absence of long-term additional effects of neurofeedback in the current study, combined with the absence of specific effects of neurofeedback over sham neurofeedback (Arnold et al., 2013; Perreau-Linck et al., 2010; van Dongen-Boomsma et al., 2013; Vollebregt et al., 2013) and the intensity of the training with a large number (20 to 40) of training sessions (Loo & Makeig, 2012), do not support implementation of theta/SMR neurofeedback as treatment for adolescents with ADHD and comorbid disorders in clinical practice.

Conclusion

The main conclusions of this thesis are:

1. Results suggest differences in underlying brain functioning related to ADHD symptomatology between adolescents with ADHD and adolescents with combined ASD+ADHD
2. Theta/SMR neurofeedback showed no additional effect over treatment as usual on behavior or neurocognitive functioning in adolescents with ADHD and comorbid disorders.

Taken together the studies in this thesis suggest that more research is needed into the psychophysiology underlying ADHD symptomatology in combined ASD+ADHD as well as ADHD. Understanding of psychophysiological mechanisms underlying ADHD symptomatology might help to develop or improve interventions for specific diagnostic groups such as adolescents with combined ASD+ADHD.

Neurofeedback has been proposed as an intervention that is potentially effective in reducing ADHD symptomatology. However, in our study, theta/SMR neurofeedback showed no additional effects over treatment as usual on behavior or neurocognitive functioning. As such, the absence of immediate or long-term additional effects of neurofeedback does not support implementation of theta/SMR neurofeedback as treatment for adolescents with ADHD and comorbid disorders in clinical practice. These results denote that using knowledge of presumed psychophysiological correlates of ADHD symptomatology for development of interventions to enduringly induce clinical relevant behavioral improvements is an even larger challenge than the arduous search for psychophysiological correlates of ADHD as such.

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NEDERLANDSE SAMENVATTING

INTRODUCTIE

Aandachtsproblemen behoren tot de kernsymptomen zowel bij adolescenten met een aandachtstekortstoornis met hyperactiviteit (Attention Deficit /Hyperactivity Disorder; ADHD), als bij adolescenten met een combinatie van autisme spectrum stoornissen (ASS) en ADHD (ASS+ADHD). Het is nog niet bekend tot op welke hoogte psychofysiologische constructen die eerder gerelateerd werden aan aandachtsproblemen op dezelfde manier voorkomen bij jongeren met ADHD en bij jongeren met een combinatie van ASS+ADHD. Het is daardoor onduidelijk of huidige behandelingen, die effectief zijn gebleken in het verminderen van ADHD-symptomen bij jongeren met ADHD, mogelijk een ander effect hebben op psychofysiologische parameters bij jongeren met ASS+ADHD en als gevolg daarvan eventueel minder effectief zijn.

Neurofeedback wordt gezien als een interventie die potentieel effectief is in het verminderen van ADHD-symptomen. Neurofeedback heeft als doel om hersenactiviteit aan te passen door operante conditionering en gelijktijdig ADHD-symptomen te verminderen (in het bijzonder het verbeteren van aandacht). Huidige resultaten zijn echter inconsistent en grote gerandomiseerde gecontroleerde studies zijn schaars. Daarnaast is nooit specifiek onderzocht of neurofeedback toegevoegde waarde heeft bovenop bestaande standaardtherapieën (in het Engels wel 'care as usual'genoemd) voor adolescenten met ADHD en bijkomende stoornissen. Dit proefschrift bestaat daarom uit twee delen. Het eerste deel richt zich op de psychofysiologische overlap en verschillen tussen adolescenten met ADHD en gecombineerde ASS+ADHD. Het tweede deel richt zich op de vraag of het mogelijk is met neurofeedback, gegeven bovenop de al geboden standaardbehandeling, het gedrag en neurocognitief functioneren te verbeteren bij deze adolescenten.

ADHD en Autisme Spectrum Stoornissen

In de 18de eeuw was Sir Alexander Crichton de eerste die een stoornis beschreef die lijkt op de huidige aandachtstekortstoornis met hyperactiviteit (ADHD) (Lange, Reichl, Lange, Tucha, & Tucha, 2010). Heden ten dage wordt ADHD gedefinieerd als een frequent voorkomend patroon van aandachtsproblemen en/of hyperactiviteit en impulsiviteitssymptomen welke interfereren met bij de ontwikkeling passende vaardigheden in het sociale, academische of werkzame leven (American Psychiatric Association, 2013). ADHD is de meest voorkomende neuropsychiatrische ontwikkelingsstoornis met een wereldwijde prevalentie van rond de 5% (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007; Willcutt, 2012). Bijkomende neuropsychiatrische stoornissen zoals leerstoornissen, gedragsstoornissen, depressie en angst worden vaker gezien bij jongeren met ADHD dan bij jongeren zonder ADHD (Larson, Russ, Kahn, & Halfon, 2011). Bij autisme spectrum stoornissen (ASS), welke gekarakteriseerd worden door aanhoudende problemen in de sociale interactie, communicatie en/of het voorkomen van stereotype gedrag, interesses en activiteiten (American Psychiatric Association, 2013), variëren de schattingen van gelijktijdig voorkomen van ADHD tussen 30% tot 78% (Gjevik, Eldevik, Fjaeran-Granum, & Sponheim, 2011; Lee & Ousley,

2006; Simonoff et al., 2008). Ondanks de observatie dat ADHD vaak gelijktijdig met ASS lijkt voor te komen, kon ADHD tot voor kort volgens het psychiatrische classificatiehandboek de DSM-IV (American Psychiatric Association 2000) niet geclassificeerd worden als een bijkomende stoornis naast ASS. De ADHD-symptomen werden gezien als onderdeel van ASS in plaats van als een bijkomende stoornis. Om te voorkomen dat patiënten met ASS en ADHD-symptomen niet in aanmerking komen voor mogelijke effectieve behandeling van ADHD (American Psychiatric Association, 2012), stellen de nieuwere classificatierichtlijnen in de DSM-V nu dat wanneer aan zowel de criteria van ASS als aan de criteria van ADHD wordt voldaan, beide diagnoses gesteld behoren te worden (American Psychiatric Association, 2013).

Op dit moment bestaat de standaardbehandeling voor ADHD-symptomen uit medicatie en/of gedragstherapie. Bewijs voor de effectiviteit van niet-farmacologische interventies zoals gedragstherapie is beperkt (Sonuga-Barke et al., 2013). Gedragstherapieën lijken effectief in het verminderen van ADHD-problemen wanneer ze geëvalueerd worden door ouders of andere mensen die zich bewust zijn van de gegeven behandeling (Sonuga-Barke et al., 2013). De effecten lijken echter te verdwijnen wanneer beoordeeld door mensen die niet op de hoogte zijn van de gegeven behandeling (Sonuga-Barke et al., 2013). Stimulantia zijn effectief in het verminderen van ADHD-klachten bij jongeren met ADHD (Faraone & Buitelaar, 2010; Greenhill et al., 2001). Voor de behandeling van ADHD bij jongeren met een combinatie van ADHD en ASS zijn stimulantia effectief, maar mogelijk in mindere mate (Cortese, Castelnau, Morcillo, Roux, & Bonnet-Brilhault, 2012; Research Units on Pediatric Psychopharmacology (RUPP) Autism Network, 2005). Daarbij komt dat voorgaande studies geen uitsluitsel geven of psychofysiologische correlaten van ADHD verschillend zijn in ASS+ADHD en ADHD. Als gevolg hiervan is het niet bekend of stimulantia, welke effectief zijn in de behandeling van ADHD (Faraone & Buitelaar, 2010; Greenhill et al., 2001), resulteren in overeenkomstige psychofysiologische effecten in gecombineerde ASS+ADHD. Verschillen in psychofysiologie tussen ADHD en ASS+ADHD kunnen een indicatie geven of stimulantia mogelijk een andere uitwerking hebben in ASS+ADHD en kunnen daardoor mogelijk helpen te verklaren waarom stimulantia minder effectief lijken te zijn in ASS+ADHD dan in ADHD.

Hoewel stimulantia effectief zijn in het verminderen van ADHD-symptomen bij een groot deel van de jongeren met ADHD (Cortese et al., 2012; Faraone & Buitelaar, 2010; Greenhill et al., 2001; RUPP, 2005), worden dosis-afhankelijke milde bijwerkingen van stimulantia, zoals verminderde eetlust, moeite met inslapen en hoofdpijn relatief vaak gerapporteerd (Cortese et al., 2012; Graham & Coghill, 2008; RUPP, 2005). Daarbij komt dat een groot deel van de adolescenten boven de leeftijd van 15 jaar op eigen initiatief stopt met het nemen van stimulantia, ondanks het aanhoudend karakter van de stoornis (Zetterqvist, Asherson, Halldner, Langstrom, & Larsson, 2012). Het ontwikkelen van nieuwe aanvullende interventies op de huidige standaard toegepaste behandelingen om ADHD-symptomen verder blijvend te verminderen, is daarom van belang. In dit opzicht wordt neurofeedback gezien als een mogelijk effectieve interventie om ADHD-symptomen te verminderen door het aanpassen van de hersenactiviteit van jongeren met ADHD (Lofthouse, Arnold, Hersch, Hurt, &

DeBeus, 2012; Moriyama et al., 2012) en ASS (Holtmann et al., 2011). Gezien de assumptie dat werkingsmechanismen van interventies zoals stimulantia en neurofeedback gebaseerd zijn op het aanpassen van afwijkende fysiologische patronen, is het tevens belangrijk om goed te doorgronden hoe fysiologie is gerelateerd aan ADHD-symptomen.

Psychofysiologie en ADHD-symptomen

Fysiologische maten zijn in eerdere studies gerelateerd aan ADHD-symptomen. Reactiviteit van de hartfrequentie is bijvoorbeeld gerelateerd aan verschillende psychologische processen, zoals aandacht, inhibitie van gedrag en sociale betrokkenheid (Porges, 2007) en daarmee aan hoofdsymptomen van ADHD. Meer specifiek worden indicaties gezien voor verhoogde parasympatische activiteit met een tragere hartslag (Negrao, Bipath, van der Westhuizen, & Viljoen, 2011) en meer variabiliteit in het hartritme (Borger & van der Meere, 2000; Borger et al., 1999; Negrao et al., 2011) bij jongeren met ADHD vergeleken met jongeren zonder ADHD. Verschillen in hersenactiviteit worden gezien in elektro-encefalogram (EEG) power spectra in ADHD, die een verhoging van theta activiteit (4-7 Hz; golven per seconde; Cortese, 2012; Loo & Makeig, 2012; Snyder & Hall, 2006), en in mindere mate, verlaagde beta activiteit (13-30 Hz; Cortese, 2012; Snyder & Hall, 2006) laten zien. Op gedragsmatig niveau is verhoogde theta activiteit gerelateerd aan verminderde waakzaamheid en weinig beta activiteit gerelateerd aan minder aandacht (Banaschewski & Brandeis, 2007). Zodoende onderschrijven deze bevindingen veronderstelde corticale onderactiviteit bij ADHD. Afwijkende, aan stimuli gerelateerde hersenactiviteit, ofwel event-related potentials (ERPs), worden ook waargenomen bij jongeren met ADHD (Du et al., 2006; Groom et al., 2010; Hermens et al., 2005; Johnstone, Barry, & Clarke, 2013; Pliszka et al., 2007). In vergelijking met normaal ontwikkelende jongeren, worden bij jongeren met ADHD kleinere amplitudes gezien in ERP-componenten die gerelateerd zijn aan aandachtsprocessen (Barry, Johnstone, & Clarke, 2003; Johnstone et al., 2013), zoals de N2, die geassocieerd is met oriëntatie en discriminatie van de stimulus (Näätänen, Simpson, & Loveless, 1982), en de P3, die geassocieerd is met selectieve aandacht en (werk)geheugen capaciteit (Polich & Herbst, 2000). Alles bij elkaar genomen lijkt ADHD samen te gaan met verminderde corticale activatieniveaus, die terug te zien zijn in de verschillende fysiologische maten.

Stimulantia welke effectief zijn in het verminderen van ADHD-symptomen van jongeren met ADHD (Faraone & Buitelaar, 2010; Greenhill et al., 2001), blijken ook de eerder genoemde afwijkende fysiologische maten gedeeltelijk te 'normaliseren'. Stimulantia verhogen de hartslag (Hammerness, Perrin, Shelley-Abrahamson, & Wilens, 2011), en het hartritme van jongeren met ADHD die stimulantia gebruiken lijkt meer op die van normaal ontwikkelende jongeren (Negrao et al., 2011). Daarnaast verlagen stimulantia de in ADHD waargenomen verhoogde theta activiteit en verhogen tegelijkertijd de beta activiteit (Clarke, Barry, Bond, McCarthy, & Selikowitz, 2002; Clarke et al., 2003; Hermens et al., 2005; Loo & Barkley, 2005). Vergelijkbaar lijken stimulantia ERP-componenten te beïnvloeden met een vergroting van N2 (Pliszka et al., 2007) en P3 (Groom et al., 2010; Hermens et

al., 2005) amplitudes na gebruik van stimulantia door jongeren met ADHD. In het algemeen lijkt het er dus op dat stimulantiagebruik door jongeren met ADHD zorgt voor fysiologische waarden die meer overeenkomen met fysiologische waarden van normaal ontwikkelende jongeren, hoewel ze geen identieke activiteitsniveaus laten zien.

Zoals eerder aangegeven, is het niet duidelijk of fysiologische patronen bij jongeren met ASS en ADHD overlappen met fysiologische patronen zoals waargenomen bij ADHD. Als fysiologische waarden overlappen, dan kan dit een indicatie zijn dat interventies die ADHD-symptomen verminderen, op eenzelfde manier werken bij jongeren met ASS+ADHD. Als fysiologische waarden welke gerelateerd zijn aan ADHD-symptomen echter anders zijn bij jongeren met een combinatie van ASS+ADHD, kan dit betekenen dat ADHD interventies mogelijk anders werken of minder effectief zijn voor jongeren met ASS+ADHD.

Neurofeedback: een overzicht

Neurofeedback is een interventie welke hersenactiviteit poogt aan te passen, door de patiënt feedback te geven over zijn eigen EEG activiteit op dat moment. Neurofeedback als een interventie voor ADHD is oorspronkelijk afgeleid van onderzoek met katten. In de zestiger jaren trainden Sterman and Wyrwicka (1967) hongerige katten om gedrag te onderdrukken en daarmee eten te verdienen. Op het moment dat het gedrag werd onderdrukt, werd in het EEG boven de sensorimotor cortex (ongeveer op het midden van het hoofd) meer activiteit waargenomen met een frequentie van 12 tot 20 golven per seconde (12-20 Hz). De activiteit werd daarom sensorimotor ritme (SMR) genoemd (Roth, Sterman, & Clemente, 1967; Sterman & Wyrwicka, 1967). Door de katten te trainen om gedrag te onderdrukken, werd zodoende indirect een verhoging in SMR activiteit, met name tussen de 12 tot 16Hz, getraind (Roth et al., 1967). In een nieuw experiment werden katten niet getraind om gedrag te onderdrukken, maar kregen de hongerige katten enkel eten wanneer het EEG meer SMR activiteit vertoonde (Sterman, Wyrwicka, & Roth, 1969). Op deze manier probeerden Sterman en collega's (1969) om SMR activiteit meer direct te trainen, in plaats van via het trainen van inhibitie. Merk op dat de katten gelijktijdig met de SMR activiteit typisch aan inhibitie gerelateerde houdingen gingen vertonen om aan eten te komen. In een daaropvolgend experiment werden drie katten, die getraind waren om SMR activiteit te vertonen in het EEG, samen met drie niet getrainde katten vergiftigd met monomethylhydrazine in opdracht van de NASA naar de toxische effecten van raketbrandstof (Sterman, LoPresti, & Fairchild, 1969). In vergelijking met de niet getrainde katten was er meer monomethylhydrazine nodig om epileptische activiteit op te wekken in de op SMR getrainde katten. Hieruit werd geconcludeerd dat SMR training protectieve waarde heeft. Hierop volgend werd de hypothese gepostuleerd dat het wellicht ook mogelijk is om hersenactiviteit te reguleren door opperante conditionering bij mensen.

Denkend aan de mogelijke protectieve eigenschappen werden de eerste experimenten met SMR training met epileptische patiënten uitgevoerd (Sterman & Friar, 1972; Sterman, Macdonald, &

Stone, 1974). Na langdurige (meer dan twee of drie maanden) biofeedback training van de SMR activiteit, lieten de patiënten een vermindering van epileptische activiteit en meer SMR activiteit zien dan voor de training (Sterman et al., 1974). Bij elkaar genomen indiceerde de resultaten dat SMR activiteit (12-16Hz) gerelateerd is aan corticale inhibitie (Roth et al., 1967; Sterman & Wyrwicka, 1967; Sterman, Wyrwicka, et al., 1969) en dat het mogelijk is het te trainen bij mensen (Sterman & Friar, 1972; Sterman et al., 1974). Overeenkomstig hiermee redeneerde Lubar en Shouse (1976) dat training met het doel SMR activiteit te verhogen ook inhibitieproblemen kan verminderen in kinderen met ADHD. De SMR training werd gecombineerd met verlagen van theta activiteit, welke negatief gerelateerd is aan waakzaamheid. Na positieve resultaat van een studie met één kind (Lubar & Shouse, 1976), volgden andere studies met meer deelnemers. Tot op heden zijn de effecten van neurofeedback het meest onderzocht en toegepast bij kinderen met ADHD.

Het meest toegepaste neurofeedback protocol voor het verminderen van ADHD-symptomen is de theta/beta training. Doel van deze training is om minder theta (4-7Hz) en meer SMR (12-15Hz) of beta (12-20Hz) activiteit te ontwikkelen (Lofthouse et al., 2012; Loo & Makeig, 2012; Moriyama et al., 2012). Dit trainingsprotocol is gebaseerd op de assumptie dat kinderen met ADHD meer theta en minder beta activiteit in het EEG laten zien dan normaal ontwikkelende kinderen (Snyder & Hall, 2006). Theta en beta zijn respectievelijk gekoppeld aan waakzaamheid en aandacht (Banaschewski & Brandeis, 2007). De rationale is dan ook dat het verminderen van theta zorgt voor verhoogde waakzaamheid en het verhogen van beta de aandacht verbetert.

In de praktijk begint een neurofeedback trainingsessie met het vastmaken van de elektrodes aan de hoofdhuid, meestal op de vertex (Cz; midden op het hoofd) en de referenties mastoïd (achter het oor). Het signaal wordt versterkt en naar een computer gestuurd. De speciaal voor neurofeedback training ontwikkelende software zet het binnenkomende signaal om en maakt het zichtbaar op de monitor van degenen die de neurofeedbacktraining geeft. De trainer kijkt naar het ruwe EEG-signaal en naar het signaal uitgesplitst in verschillende frequentiebanden tussen de 4Hz en 32Hz. Verschillende frequentiebanden kunnen gelijktijdig getraind worden. In het geval van theta/beta training is de software geprogrammeerd met het doel SMR of beta te versterken en theta of andere frequentiebanden te onderdrukken. Gebaseerd op het binnenkomende EEG-signaal, worden de grenswaarden per frequentieband bepaald. Als het signaal binnen de grenswaarde valt voor elke frequentieband, dan wordt het signaal goedgekeurd en wordt de patiënt beloond met positieve feedback. Op hetzelfde moment kijkt de patiënt naar een monitor welke een visuele representatie geeft van zijn of haar eigen EEG activiteit. De visuele representatie kan worden gegeven in de vorm van een film of een spelachtige situatie. In het geval van de film beïnvloedt het EEG signaal de kwaliteit van de film –beeld en geluid-. In de spelachtige situatie beïnvloedt de hersenactiviteit de beelden, het geluid en de scores. Op deze manier worden de verschillende frequentiebanden versterkt of onderdrukt door middel van operante conditionering in ongeveer 20 tot 40 sessies.

Een speciale vorm van neurofeedback is de training van slow cortical potentials (SCPs) ofwel langzame corticale golven. SCPs zijn heel langzame potentialen (<0.1Hz). Een negatieve (naar beneden

buigende) hele langzame golf is geassocieerd met verhoogde corticale activiteit en gerelateerd aan meer efficiënte reacties in gedrag. Een positieve (omhoog buigende) hele langzame hersengolf is geassocieerd met een verlaging van de corticale activiteit en minder efficiënte reacties in gedrag (Birbaumer, Elbert, Canavan, & Rockstroh, 1990). Het idee is dat de patiënten leren om controle te krijgen over het activiteitsniveau van de hersenen, door zich afwisselend te richten op het verhogen en verlagen van de hersenactiviteit. Implementatie van SCP-training komt in de praktijk nog weinig voor, gedeeltelijk omdat SCPs moeilijker betrouwbaar te meten zijn.

Effectiviteit van neurofeedback als behandeling bij ADHD

De eerste niet-gerandomiseerde studies naar de effectiviteit van neurofeedback bij jongeren met ADHD vergelijken standaard behandeling, inclusief stimulantia, met neurofeedback, soms als aanvullende therapie op de standaard behandeling. In het algemeen lieten deze studies vergelijkbare verbeteringen in aandacht zien, zoals gemeten met gedragsvragenlijsten en neurocognitieve testen, voor zowel jongeren die neurofeedback training kregen als voor jongeren die stimulantia namen (Fuchs, Birbaumer, Lutzenberger, Gruzelier, & Kaiser, 2003; Rossiter & La Vaque, 1995). Neurofeedback leek zelfs van aanvullende waarde op het nemen van stimulantia (Monastra, Monastra, & George, 2002). Vergeleken met een combinatie van stimulantia en ouder- en school- educatie, lieten jongeren die ook neurofeedback kregen meer hersenactiviteit zien, verbeterde aandacht en verminderde hyperactief en impulsief gedrag thuis en op school. De studie van Monastra en collega's (2002) toonde dat de jongeren die neurofeedback hadden gekregen, een jaar na de training nog altijd minder ADHD-symptomen lieten zien dan de jongeren die alleen de standaard behandeling hadden gekregen.

De studies die volgden hadden gerandomiseerd gecontroleerde designs (randomized controlled trials; RCT) en toonden ook positieve effecten van neurofeedback training. De grootste gerandomiseerde studie met 94 kinderen tussen de 8 en 12 jaar liet zien dat neurofeedback (n=59) effectiever was in het verminderen van ADHD-symptomen dan gecomputeriseerde aandacht training (n=35) tot een half jaar na de behandeling (Gevensleben et al., 2010; Gevensleben, Holl, Albrecht, Vogel, et al., 2009). Bij deze studie werd van frontaal naar pariëtaal een steeds sterkere vermindering in theta activiteit waargenomen in de groep die neurofeedback had gekregen. De vermindering in theta activiteit was tevens gerelateerd aan een vermindering van ADHD-symptomen zoals door de ouders gerapporteerd (Gevensleben, Holl, Albrecht, Schlamp, et al., 2009). De studie van Duric en collega's (2012) toonde gelijkwaardige verbetering van aandacht op gedragsvragenlijsten over de tijd voor jongeren met ADHD welke waren behandeld met neurofeedback (n=30), stimulantia (n=31) of een combinatie van stimulantia en gedragstherapie (n=30). Een kleinere studie met een gerandomiseerd design liet eveneens vergelijkbare verbeteringen in aandacht zien voor neurofeedback (n=12) en stimulantia (n=11) (Meisel, Servera, Garcia-Banda, Cardo, & Moreno, 2013). Overeenstemmend met

de niet gecontroleerde studies, laten deze RCTs gelijkwaardige vooruitgang zien voor neurofeedback en stimulantia.

Meer recente geblindeerde RCT studies laten echter in het algemeen geen meerwaarde zien van neurofeedback ten opzichte van placebo-neurofeedback voor het verminderen van ADHD-symptomen (Arnold et al., 2012; Perreau-Linck, Lessard, Levesque, & Beauregard, 2010; van Dongen-Boomsma, Vollebregt, Slaats-Willemse, & Buitelaar, 2013; Vollebregt, van Dongen-Boomsma, Buitelaar, & Slaats-Willemse, 2013). De meest optimistische studie is een enkelvoudig geblindeerde studie waarbij jongeren met ADHD die neurofeedback training volgden (*n*=18) meer verbeterden op aandacht zoals gerapporteerd door ouders en op neurocognitieve maten zoals reactietijd en accuraatheid, dan de jongeren die elektromyografie (EMG) biofeedback training kregen (*n*=17) (Bakhshayesh, Hansch, Wyschkon, Rezai, & Esser, 2011). De andere geblindeerde studies vonden geen verschillen tussen neurofeedback en placebo-neurofeedback in vermindering van ADHD-symptomen bij jongeren met ADHD (Arnold et al., 2012; Perreau-Linck et al., 2010; van Dongen-Boomsma et al., 2013). Het aantal deelnemers bij deze onderzoeken was echter relatief klein, met deelnemers ingedeeld voor neurofeedback versus placebo-neurofeedback van respectievelijk *n*=4 tegen *n*=4 (Perreau-Linck et al., 2010), *n*=25 tegen *n*=11 (Arnold et al., 2012) en *n*=22 tegen *n*=19 (van Dongen-Boomsma et al., 2013). Het lijkt erop dat eerder gerapporteerde positieve uitkomsten van niet-placebo gecontroleerde studies naar de effectiviteit van neurofeedback bij ADHD het resultaat zijn van niet-specifieke behandeleffecten zoals motivatie en verwachting bij de jongeren en de ouders, de technologische setting met een behoorlijk medische uitstraling en het grote aantal trainingssessies met een therapeut.

Er zijn minder klinische effectiviteitsstudies uitgevoerd naar de werking van neurofeedback bij ASS dan bij ADHD. De meest gebruikte neurofeedback protocollen die bij ASS worden toegepast betreffen training van frequentiebanden (Holtmann et al., 2011) gelijkend op de protocollen zoals toegepast bij ADHD met inhibitie van theta (4-7 Hz) en versterking van SMR (12-15 Hz) (Coben, Linden, & Myers, 2010) of onderdrukking van het Mu ritme (8-13Hz) (Coben et al., 2010; Holtmann et al., 2011). De review van Holtmann en collega's (2011) concludeert dat neurofeedback niet effectief lijkt voor ASS kenmerken, maar mogelijk wel effectief kan zijn voor het verminderen van bijkomende ADHD-symptomen.

Claims over de effectiviteit van neurofeedback voor de behandeling van ADHD lopen uiteen van 'effectief en specifiek' (Arns, de Ridder, Strehl, Breteler, & Coenen, 2009) en 'mogelijk effectief' (Lofthouse et al., 2012; Moriyama et al., 2012), tot niet effectief met geblindeerde opzet van de studie (Sonuga-Barke et al., 2013). De range van effectiviteitsbeoordelingen is zo breed doordat de meeste studies gehinderd zijn door verschillende methodologische tekortkomingen: het grootste deel van de studies was niet gerandomiseerd, groepsgrootten waren relatief klein en/of er was niet gecontroleerd voor niet-specifieke behandeleffecten. Onlangs gemaakte schattingen zijn daarom conservatiever (Gevensleben, Rothenberger, Moll, & Heinrich, 2012; Lofthouse et al., 2012; Loo & Makeig, 2012; Moriyama et al., 2012; Sonuga-Barke et al., 2013). Tekortkomingen in de designs van voorgaande onderzoeken en missende kennis over mogelijke (negatieve) bijwerkingen zorgen ervoor dat er geen

harde conclusies kunnen worden getrokken. Meer gecontroleerd onderzoek is daarom nodig om te kijken of er specifieke patiëntgroepen zijn die profiteren van neurofeedback en of dit afhankelijk is van het soort toegepaste neurofeedback training protocol (Gevensleben et al., 2012; Lofthouse et al., 2012). Verder is het van belang dat er onderzoek wordt gedaan om te zien of neurofeedback van aanvullende waarde is op multimodale behandelprotocollen (Gevensleben et al., 2012). Bovenal is het van belang de waarde van neurofeedback in de klinische praktijk te onderzoeken, waar meer heterogene populaties van jongeren met ADHD worden gezien. Dienovereenkomstig is het van belang dat jongeren met ADHD en bijkomende stoornissen, zoals ASS, welke behandeling behoeven voor ADHD-symptomen, ook tot de studie worden toegelaten, zodat de klinische praktijk zo goed mogelijk wordt nagebootst.

De onderwerpen van dit proefschrift

Dit proefschrift heeft twee hoofdonderwerpen. Het eerste onderwerp van het proefschrift betreft het verkennen van psychofysiologie in adolescenten met ADHD en ASS+ADHD en de mogelijke klinische implicaties hiervan. Het tweede onderwerp van het proefschrift omvat het onderzoek naar de aanvullende waarde van neurofeedback op de huidige standaard toegepaste behandeling om gedrag en neurocognitief functioneren van adolescenten met ADHD te verbeteren. Overeenkomstig worden in het eerste deel van het proefschrift overlap en verschillen in psychofysiologische maten tussen adolescenten met ADHD en adolescenten met een combinatie van ADD+ADHD beschreven. In het tweede gedeelte van het proefschrift wordt de aanvullende waarde van neurofeedback op de huidige standaard toegepaste behandeling voor adolescenten met ADHD en andere stoornissen onderzocht.

SAMENVATTING

Deel 1: Psychofysiologie in adolescenten met ADHD en ASS+ADHD

ADHD is een van de meest voorkomende neuropsychiatrische stoornissen met een prevalentie van rond de 5% (Polanczyk et al., 2007; Willcutt, 2012). Daarnaast vertoont een groot aantal jongeren met ASS ook ADHD-symptomen. Fysiologische maten, zoals reactiviteit van het hart, EEG power spectra en ERP componenten zijn gerelateerd aan ADHD-symptomen. In het eerste deel van dit proefschrift is verkend of psychofysiologische correlaten van ADHD overlappen of verschillen tussen adolescenten met ADHD en adolescenten met een combinatie van ASS en ADHD, met en zonder gebruik van stimulantia.

Als eerste is er gekeken naar hartactiviteit bij adolescenten met ADHD en adolescenten met ASS+ADHD. Afwijkende hartritme activiteit, wijzend op verhoogde parasympatische activiteit zoals lage hartslag (Negrao et al., 2011) en meer variabiliteit in het hartritme (Borger & van der Meere, 2000; Borger et al., 1999; Negrao et al., 2011) lijken gerelateerd aan ADHD. ASS daarentegen is geassocieerd met een verhoging in sympathische activiteit (Bal et al., 2010; Daluwatte et al., 2012; Van Hecke et al., 2009). De verwachting was daarom dat adolescenten met ASS+ADHD meer tekenen van verhoogde sympathische en minder parasympatische activiteit zouden vertonen dan adolescenten met ADHD. De adolescenten met ADHD en de adolescenten met ASS+ADHD vertoonden echter geen verschillen op de hartritme maten. Adolescenten die

stimulantia namen, toonden verminderde adaptatie van de LF/HF ratio en snellere reactietijden dan adolescenten die geen stimulantia namen, onafhankelijk van de diagnose die ze hadden. Deze studie wijst op overlap in hartritme activiteit tussen adolescenten met ADHD en adolescenten met ASS+ADHD.

Als tweede zijn mogelijke overlap en verschillen in theta en beta power spectra tussen adolescenten met ADHD en ASS+ADHD verkend. In tegenstelling tot de hartactiviteit, lieten EEG power spectra verschillen zien tussen adolescenten met ADHD en adolescenten met ASS+ADHD. Met de ogen open en tijdens het maken van een aandachtstaak lieten de adolescenten met ADHD meer theta activiteit zien dan adolescenten met ASS+ADHD, ongeacht of ze stimulantia gebruiken. Met de ogen dicht is de theta activiteit gelijk in beide groepen. Verhoogde theta tijdens rustcondities (Cortese, 2012; Loo & Makeig, 2012; Snyder & Hall, 2006) is een van de meest robuuste bevindingen bij ADHD. Deze verschillen in theta activiteit wijzen erop dat adolescenten met ASS+ADHD minder fysiologische kenmerken in het EEG vertonen die normaal geassocieerd worden met ADHD, ondanks de overlap in aandachtsproblemen in beide groepen.

Als derde is gekeken naar stimuli-gerelateerde hersenactiviteit, ERPs, tijdens een auditieve aandachttaak. Psychofysiologische indices van hersenfunctioneren, zoals ERP componenten, zijn gerelateerd aan cognitief functioneren, zoals aandacht, response selectie, inhibitie en response monitoring (Johnstone et al., 2013). ERP componenten verschilden afhankelijk van de gestelde diagnose en van het gebruik van stimulantia. Adolescenten met ASS+ADHD die geen stimulantia gebruikten, hadden een kleinere N2 amplitude dan degenenn die wel stimulantia gebruikten. Bij adolescenten met ADHD was er geen verschil tussen degenen die wel en geen stimulantia gebruikten. De kleinere N2 amplitude suggereert dat adolescenten met ASS+ADHD die geen stimulantia gebruikten meer moeite hebben om het verschil waar te nemen tussen twee verschillende stimuli (piepjes) dan adolescenten met ASS+ADHD die wel stimulantia gebruiken. Een andere bevinding in dit onderzoek was dat adolescenten met ADHD wanneer zij stimulantia gebruikten een vroegere N1 piek lieten zien, waar adolescenten met ASS+ADHD wanneer ze stimulantia gebruiken juist een latere N1 piek lieten zien ten opzichte van adolescenten die geen stimulantia gebruiken. Deze resultaten tonen dat ERP activiteit afhankelijk is van de vastgestelde diagnose, ADHD of ASS+ADHD, en van het gebruik van stimulantia.

Samengenomen laten de resultaten van het eerste deel van het proefschrift zien dat er ondanks gedragsmatige overlap en overlap in hartactiviteit tussen adolescenten met ADHD en adolescenten met ASS+ADHD, verschillen zijn in hersenactiviteit. Deze verschillen zijn van belang, omdat het indicaties zijn voor de mogelijkheid dat behandeling ontwikkeld voor ADHD anders werkt voor adolescenten met ASS+ADHD dan voor adolescenten met alleen ADHD.

Deel 2: De aanvullende waarde van neurofeedback op huidig toegepaste behandelingen

Neurofeedback wordt gezien als een potentieel effectieve behandeling voor het verminderen van ADHD-symptomen, voornamelijk aandachtsproblemen. Neurofeedback poogt hersenactiviteit aan te passen doormiddel van operante conditionering door het geven van feedback over de EEG activiteit van patiënten om zodoende het gedrag te verbeteren. In het algemeen laten jongeren met ADHD meer theta (Cortese, 2012; Loo & Makeig, 2012; Snyder & Hall, 2006) en minder beta (Cortese, 2012; Snyder & Hall, 2006) activiteit zien in vergelijking met normaal ontwikkelende jongeren. Het meest

toegepaste neurofeedback training protocol is daarom de theta/beta training, welke als doel heeft theta (4-7Hz) te verminderen en SMR (12-15Hz) of beta (12-20Hz) activiteit te versterken (Lofthouse et al., 2012; Loo & Makeig, 2012; Moriyama et al., 2012). In het algemeen omvat een complete neurofeedback behandeling ongeveer 20 tot 40 sessies (Loo & Makeig, 2012). In het tweede deel van dit proefschrift is gekeken naar de waarde van neurofeedback als aanvulling op de huidige standaard toegepaste behandelingen om gedrag en neurocognitief functioneren te verbeteren bij adolescenten met ADHD en bijkomende stoornissen.

Door middel van een multicenter onderzoek met een gerandomiseerd gecontroleerd design, zijn 90 mannelijke adolescenten met een DSM-IV diagnose ADHD geloot om al dan niet neurofeedback te krijgen naast de standaardbehandeling. Neurofeedback behelsde ongeveer 37 sessies theta/SMR-training op Cz (op het midden van het hoofd). De interventieperiode duurde ongeveer 25 weken. In totaal zijn 71 adolescenten (gemiddelde leeftijd van ongeveer 16 jaar) vergeleken op maten van gedrag en neurocognitief functioneren, zowel voor als na de interventieperiode. Zestig adolescenten werden op dezelfde maten nogmaals vergeleken één jaar na de interventieperiode.

Als eerste is de waarde van neurofeedback als aanvullende behandeling op de momenteel toegepaste behandeling op gedragsmaten bekeken direct na de interventieperiode. Gedragsproblemen, zoals onoplettendheid en hyperactiviteit en impulsiviteit, waren verminderd voor alle adolescenten met ADHD gedurende de interventieperiode. Er waren echter geen verschillen tussen de 45 adolescenten die neurofeedbacktraining hadden gevolgd als aanvulling op de standaardbehandeling en de adolescenten die alleen standaardbehandeling hadden ontvangen. Het gebruik van stimulantia of de aanwezigheid van een ASS diagnose had geen effect op de gerapporteerde vermindering van gedragsproblemen met het verstrijken van de tijd. Ook de rapportage van bijwerkingen was gelijk in beide groepen. Hoofdpijnfrequentie was afhankelijk van het gebruik van stimulantia: adolescenten die geen stimulantia gebruiken, rapporteerden na de interventieperiode een vermindering van het aantal keer dat ze hoofdpijn hadden gekregen. De adolescenten die wel stimulantia gebruiken, rapporteerden geen verminderingen in hoofdpijnfrequentie. Samenvattend kan gezegd worden dat op basis van het gerapporteerde gedrag de combinatie van neurofeedback en standaardbehandeling net zo effectief is als alleen standaardbehandeling. Er is geen toegevoegde waarde van neurofeedback op gedrag gevonden.

Na het bestuderen van effecten op gedrag zijn mogelijke aanvullende effecten van neurofeedback op neurocognitief functioneren onderzocht. Voor en direct na de interventieperiode werden de adolescenten vergeleken op verschillende neurocognitieve maten: de 'd2 aandacht test', 'getallen reeksen achteruit', de 'Stroop kleur-woord' test en de 'Tower of London'. Resultaten toonden verbetering op maten van aandacht direct na de interventieperiode voor alle adolescenten met ADHD. De adolescenten hadden minder tijd nodig om informatie te verwerken en de taak uit te voeren met dezelfde accuratesse. Indices van werkgeheugen en planning bleven gelijk. De 45 adolescenten die neurofeedbacktraining hadden gekregen als aanvullende behandeling presteerden hetzelfde als de 26 adolescenten die geen neurofeedback hadden gekregen. Net als bij de gedragsmaten zijn er geen

aanvullende effecten van neurofeedback op de standaardbehandeling gevonden voor neurocognitief functioneren.

Een jaar na de interventie zijn 60 adolescenten nogmaals getest. Deze adolescenten zijn wederom vergeleken om te kijken naar de aanvullende waarde van neurofeedback op de standaardbehandeling op de lange termijn. Er is gekeken naar vermindering van ADHD-symptomen door middel van zelfgerapporteerd gedrag en neurocognitieve maten. Alle adolescenten met ADHD rapporteerden 1 jaar na de interventie minder gedragsproblemen dan voor de interventieperiode. De adolescenten werden ook sneller in het uitvoeren van de neurocognitieve taken. Er was geen verschil in de vooruitgang over de tijd tussen de 41 adolescenten die neurofeedback hadden ontvangen als aanvullende behandeling en de 19 adolescenten die geen neurofeedback hadden gevolgd. Evenals de resultaten in gedrag en neurocognitief functioneren direct na de interventieperiode, tonen de langetermijnresultaten geen aanvullende waarde van neurofeedback.

In het tweede deel van dit proefschrift is de aanvullende waarde van neurofeedback op de momenteel toegepaste standaardbehandeling bij adolescenten met ADHD onderzocht. Er is geen aanvullende waarde van neurofeedback gevonden op gedrag of neurocognitief functioneren bij adolescenten met ADHD en bijkomende stoornissen direct na de interventie en een jaar na de interventie. De huidige resultaten laten geen robuuste aanvullende waarde van neurofeedback op korte en lange termijn zien en ondersteunen daarmee niet het gebruik van theta/SMR neurofeedback als aanvullende behandeling om blijvende verbeteringen in gedrag of neurocognitief functioneren van adolescenten met ADHD en bijkomende stoornissen te bewerkstelligen in de klinische praktijk.

DISCUSSIE

Twee van een soort: ADHD en ASS+ADHD

Het eerste deel van het proefschrift wijst erop dat er, naast overlap in gedrag en hartslag maten bij adolescenten met ADHD en adolescenten met ASS+ADHD, verschillen zijn in hersenactiviteit. Deze verschillen zijn van belang, omdat het bestaan van verschillen betekenen dat behandelingen die ontwikkeld zijn voor ADHD, misschien anders werken voor adolescenten met ASS+ADHD dan voor adolescenten met ADHD.

De veronderstelling voor hartritme activiteit was dat ADHD geassocieerd is met tekenen van verhoogde parasympatische activatie, terwijl ASS voorheen geassocieerd is met tekenen van verhoogde sympathische activatie. De verwachting was daarom dat de adolescenten met ASS+ADHD meer sympathische en minder parasympatische activatie tonen dan adolescenten met ADHD. Hartritme maten waren echter gelijk voor de adolescenten met ASS+ADHD en de adolescenten met ADHD. Een mogelijke verklaring voor deze bevinding is dat er psychofysiologische constructen zijn welke gerelateerd zijn aan de ADHD-symptomen, die verantwoordelijk zijn voor de overlap in hartritme activiteit tussen ADHD en ASS+ADHD.

In het functioneren van de hersenen zijn er naast overlap ook verschillen gevonden tussen de twee diagnose groepen. Het meest opvallende resultaat was dat adolescenten met ADHD meer theta activiteit hebben dan adolescenten met ASS+ADHD als ze hun ogen open hebben of tijdens het maken van een taak. Daarnaast bleek dat voor adolescenten met ADHD veel theta in rust conditie met de ogen open gerelateerd is aan slechtere prestatie op een aandachttaak. Bij adolescenten met ASS+ADHD was deze relatie niet aanwezig. Verhoogde theta is een van de meest robuuste bevindingen bij ADHD (Cortese, 2012; Loo & Makeig, 2012; Snyder & Hall, 2006). Aangezien theta (4-7Hz) een negatieve relatie heeft met waakzaamheid (Banaschewski & Brandeis, 2007), kan dit betekenen dat verhoogde theta en verlaagde waakzaamheid een betere verklaring biedt voor aandachtsproblemen in adolescenten met ADHD dan in adolescenten met ASS+ADHD. De aandachtsproblemen in ASS+ADHD zijn mogelijk het resultaat van ander hersendisfunctioneren, zoals abnormale neuronale connectiviteit (Billeci et al., 2013; Coben, Clarke, Hudspeth, & Barry, 2008) en problemen met "top-down" verwerking (Gomot & Wicker, 2012) –een actieve vorm van verwerking waarbij voorheen opgedane kennis wordt gebruikt om een inschatting te maken van toekomstige doelen -, in plaats van verminderde frontocentrale activiteit op zichzelf. De uitkomsten van de ERP componenten wijzen eveneens op problemen met het verwerken van informatie in ASS+ADHD. De adolescenten met ASS+ADHD die geen stimulantia gebruiken, lieten een kleinere amplitude van de N2 component zien als reactie op stimuli die actie behoeven, dan adolescenten met ASS+ADHD die wel stimulantia gebruiken. Dit verschil was niet aanwezig tussen adolescenten met ADHD die wel of geen stimulantia gebruiken. De kleinere amplitude van de N2 component op doel stimuli geeft een voorzichtige indicatie dat adolescenten met ASS+ADHD die geen stimulantia gebruiken, meer problemen hebben met discriminatie van stimuli.

De verwachting was dat stimulantia normaliserend werken op de psychofysiologische karakteristieken van ADHD. Daarom was de verwachting was dat de adolescenten die stimulantia gebruiken minder neurocognitieve en fysiologische tekenen vertonen die in het algemeen worden geassocieerd met ADHD dan de adolescenten die geen stimulantia gebruikten, ongeacht de diagnose (ADHD of ASS+ADHD). De adolescenten die stimulantia gebruikten reageerden inderdaad sneller en minder variabel op stimuli dan adolescenten die geen stimulantia gebruikten, onafhankelijk van de diagnose. Ook in de hartslag maten is verschil gevonden voor het gebruik van stimulantia: adolescenten die stimulantia gebruiken hadden een hogere LF/HF ratio in rust conditie dan adolescenten die geen stimulantia gebruikten. Tijdens het uitvoeren van een taak was de LF/HF ratio gelijk voor adolescenten die stimulantia gebruikten en zij die dat niet deden. Als gevolg hiervan was de aanpassing van de LF/HF ratio, die normaal een verhoging laat zien van rust naar taak condities, verminderd voor adolescenten die stimulantia gebruiken. Een vermindering van parasympatische activiteit bij ADHD kan in het algemeen worden gezien als een teken van normalisatie. Een vermindering van autonome modulatie kan mogelijk minder wenselijk zijn. Het is niet duidelijk wat de implicaties zijn voor het dagelijks leven als adolescenten die stimulantia gebruiken minder in fysiologisch opzicht kunnen wisselen tussen rust en taken die aandacht vereisen.

Het is opvallend dat er geen verschillen waren in theta en beta activiteit afhankelijk van het gebruik van stimulantia. In het algemeen wordt er een daling in theta en verhoging van beta gezien bij jongeren met ADHD na het gebruik van stimulantia (Clarke et al., 2002; Clarke et al., 2003; Hermens et al., 2005; Loo & Barkley, 2005). Hierbij dient opgemerkt te worden dat, ook al worden theta en beta beïnvloed door stimulantia, de jongeren met ADHD die stimulantia gebruiken nog altijd niet gelijkwaardige niveaus van theta en beta bereiken ten opzichte van normaal ontwikkelende jongeren (Clarke et al., 2002; Clarke et al., 2003). Verschillen in leeftijd tussen de adolescenten die wel en geen stimulantia gebruiken, hebben mogelijk bijgedragen aan de afwezigheid van verschillen met betrekking tot stimulantia gebruik. Gemiddeld genomen waren de adolescenten die geen stimulantia gebruikten ouder dan degenen die wel stimulantia gebruikten. Daar ouder worden (Segalowitz, Santesso, & Jetha, 2010) evenals het gebruik van stimulantia (Clarke et al., 2002; Clarke et al., 2003; Hermens et al., 2005; Loo & Barkley, 2005) beide resulteren in verlaging van theta activiteit, is het mogelijk dat de twee effecten elkaar in evenwicht hebben gehouden.

Stimulantia zijn in het algemeen ook van invloed op ERP componenten, welke terug te zien zijn in grotere N2 (Pliszka et al., 2007) en P3 (Groom et al., 2010; Hermens et al., 2005) amplitudes na het gebruik van stimulantia door jongeren met ADHD. Overeenkomstig met deze veronderstelling vonden we grotere N2 amplitudes voor adolescenten met ASS+ADHD die stimulantia gebruikten in vergelijking met degenen die geen stimulantia gebruiken. Verrassend genoeg was er geen verschil voor het gebruik van stimulantia voor de adolescenten met ADHD. Daarnaast vonden wij, net als de studie van Groen en collega's (2008), geen grotere P3 amplitude voor de adolescenten die stimulantia gebruiken dan voor degenen die geen stimulantia gebruiken. Er is echter een duidelijk verschil tussen de studies. De studies die een verschil vonden in P3 amplitude vergeleken dezelfde jongeren met ADHD, met en zonder stimulantia (Groom et al., 2010; Hermens et al., 2005), terwijl bij de studie van Groen en collega's (2008) en onze studie een groep jongeren die wel stimulantia gebruikte werd vergeleken met een groep die geen stimulantia gebruikte. Bij vergelijking van twee verschillende (relatief kleine) groepen, zoals bij onze studie zijn er altijd verschillen tussen personen die effect hebben op de uitkomsten. Verschillen tussen personen kunnen dan beter gecontroleerd worden wanneer er binnen een groep patiënten in verschillende situaties gekeken wordt naar uitkomsten: elke patiënt controleert dan als het ware voor zijn eigen variantie. Hierdoor kunnen verschillen voor stimulantia gebruik binnen een groep patiënten mogelijk beter worden aangetoond dan verschillen tussen twee groepen patiënten.

Stimulantia hadden eveneens invloed op de latentie tijden van de N1 piek welke afhankelijk waren van de diagnose. Adolescenten met ASS+ADHD die stimulantia gebruikten hadden langere N1 latentie tijden dan degenen die geen stimulantia gebruikten. Een tegenovergesteld patroon zagen we bij de adolescenten met ADHD: degenen die stimulantia namen hadden een kortere N1 latentie tijd dan degenen die geen stimulantia gebruikten. Kortere latentie tijden worden in het algemeen gezien als een indicatie dat informatie efficiënter verwerkt wordt. De resultaten lieten echter zien dat een langere N1 latentie geassocieerd was met een grotere N1 amplitude. Een latere N1 piek was zelfs gerelateerd aan

minder variabele reactie tijden bij adolescenten met ASS+ADHD. Deze resultaten toonden dus dat de latere N1 piek gerelateerd is met een meer consistent reactie patroon op doel stimuli, met name voor adolescenten met ASS+ADHD.

De studies uit het eerste deel van dit proefschrift laten verschillen in hersenactiviteit zien tussen adolescenten met ADHD en ASS+ADHD. De verschillen werden gevonden in een klinische groep van adolescenten met ADHD-symptomen die voldoende zijn voor een DSM-IV diagnose ADHD. Stimulantia gebruik was toegestaan en werd voortgezet op de dagen waarop de jongeren gezien werden voor het afnemen van de vragenlijsten, cognitieve testen en fysiologische metingen. Op deze manier weerspiegelt de onderzochte groep de klinische praktijk. Dit zorgt er echter ook voor dat de onderzochte groep erg heterogeen is met betrekking tot diagnoses (ADHD of ASS+ADHD), stimulantia gebruik en leeftijd. Meer systematisch onderzoek naar de psychofysiologische aspecten van ADHD en ASS+ADHD en de implicaties voor de klinische praktijk zijn daarom noodzakelijk. Replicatie van de psychofysiologische resultaten van de huidige studie, met een grotere groep zijn nodig, bij voorkeur opgezet met een gerandomiseerd gecontroleerd design met dubbel-blind placebo-gecontroleerde titratie van stimulantia en een baseline meting met adolescenten die geen stimulantia gebruiken en gediagnosticeerd zijn met ADHD en ASS+ADHD. Daarnaast is een controle groep die enkel gediagnosticeerd is met ASS en een groep met normaal ontwikkelende adolescenten van belang om te kijken welke psychofysiologische aspecten typerend zijn voor de normale ontwikkeling, welke voor ADHD en welke voor ASS.

Samengevat wijzen de resultaten uit het eerste deel van dit proefschrift erop dat waar gedrag en hartritme maten overlappen tussen adolescenten met ADHD en ASS+ADHD, er mogelijk verschillen zijn in onderliggend hersenfunctioneren gerelateerd aan ADHD-symptomen. Klinische implicaties van deze psychofysiologische verschillen en reactie op het gebruik van stimulantia moeten in de toekomst verder worden onderzocht om de behandeling van ADHD als bijkomende stoornis van ASS te optimaliseren.

Neurofeedback: Ingrediënten van effectiviteit

In het tweede deel van dit proefschrift hebben we de waarde van neurofeedback als aanvullende behandeling om ADHD-symptomen te verminderen en neurocognitief functioneren te verbeteren voor adolescenten met ADHD en bijkomende stoornissen onderzocht. Er zijn geen aanvullende effecten voor neurofeedback op korte of lange termijn gevonden om gedrag of neurocognitief functioneren te verbeteren bij jongeren met ADHD. De resultaten van het huidige onderzoek onderschrijven daarmee niet het gebruik van theta/SMR neurofeedback als aanvullende behandeling om gedrag of neurocognitief functioneren te verbeteren in adolescenten met ADHD en comorbide stoornissen in de klinische praktijk.

De conclusie van een meta-analyse uit 2009 was dat neurofeedback als behandeling voor ADHD "effectief en specifiek" is (Arns et al., 2009). De geschatte effectgrootten varieerden van gemiddeld voor hyperactiviteit tot groot voor het verminderen van aandachtsproblemen en impulsiviteit (Arns et al., 2009). In de jaren daarna is er steeds meer interesse getoond in deze niet-farmacologische interventie. Dit resulteerde in verschillende reviews in 2012 die erop wezen dat neurofeedback een mogelijk effectieve behandeling is voor ADHD (Gevensleben et al., 2012; Lofthouse et al., 2012; Moriyama et al., 2012). Een andere review was minder positief met betrekking tot theta/beta neurofeedback, en stelde dat: *de staat van de huidige gepubliceerde peer reviewed literatuur over theta/beta training, zoals het op dit moment is, niet ondersteunend is voor het gebruik van theta/beta training zelfs niet als een aanvullende behandeling* (Loo & Makeig, 2012). Een nieuwe meta-analyse gepubliceerd in 2013 laat zien dat de effectiviteit van neurofeedback zakt naar niet-significante niveaus wanneer er sprake is van een geblindeerde meting (Sonuga-Barke et al., 2013). Overeenkomstig gaven de resultaten van een systematische review geen indicaties dat neurofeedback effectief is om neurocognitief functioneren in ADHD te verbeteren (Vollebregt et al., 2013). Inschattingen van de effectiviteit van neurofeedback als behandeling van ADHD-symptomen lopen dus uiteen van "effectief en specifiek" tot "niet effectief".

Kijkend naar de brede range van schattingen met betrekking tot de effectiviteit van neurofeedback binnen vier jaar tijd, is het een gepaste vraag om te stellen waar deze verschillen vandaan komen. Mogelijk ligt de verklaring in de methodologische problemen die veel studies naar de effectiviteit van neurofeedback parten hebben gespeeld. Niet alleen met betrekking tot de grote verschillen tussen studies in de opzet van het design, maar ook met betrekking tot het toegepaste neurofeedback training protocol. Om het geheel af te bakenen wordt in deze discussie alleen gekeken naar de veel toegepaste frequentie–vooral theta/beta- training protocollen die zich richten op patiënten met ADHD.

De eerste niet gerandomiseerde studies die neurofeedback met andere behandelingen vergeleken (e.g. Fuchs et al., 2003; Monastra et al., 2002) lieten positieve resultaten voor neurofeedback zien. Deze studies controleerden echter niet voor niet-specifieke behandeleffecten. Zo is het bijvoorbeeld mogelijk dat ouders die een voorkeur hebben voor een intensieve niet-farmacologische behandeling zoals neurofeedback, wellicht meer aanmoediging bieden aan hun kind met ADHD om te

veranderen. In het algemeen bestaat een complete neurofeedback training uit ongeveer 20 tot 40 sessies. De ouders die hun kind elke week twee of drie keer naar therapie kunnen en willen brengen, zijn mogelijk ook beter in staat een meer gestructureerde en voorspelbare omgeving voor het kind te scheppen. Daarnaast maakt de geïnvesteerde tijd in de behandeling door het kind, de therapeut en de ouders, dat de ouders meer geneigd kunnen zijn om positieve verandering in het gedrag van het kind te willen zien. Naast niet-specifieke effecten op gedragsmetingen beïnvloed door vooringenomenheid van de ouders, spelen maturatie en oefeneffecten mogelijk een rol bij het waarnemen van verbeteringen bij de uitvoer van neurocognitieve taken mettertijd.

Om beter te controleren voor deze niet-specifieke effecten van tijdsinvestering en voorkeur, zijn er daarna studies met een gerandomiseerd design, zogenaamde randomized controlled trials (RCT), uitgevoerd. Ouders kregen niet langer de mogelijkheid om te kiezen voor een specifieke behandeling voor hun kind, zoals in de eerste studies. In plaats daarvan konden ouders en kinderen enkel kiezen om wel of niet deel te nemen aan een studie. Ze wisten van te voren niet bij welke behandeling ze zouden worden ingedeeld. In een van de eerste grote RCT studies werden kinderen met ADHD die geen stimulantia gebruiken, ingeloot voor neurofeedback (n=59) of een gecomputeriseerde aandacht training (n=35) (Gevensleben, Holl, Albrecht, Vogel, et al., 2009). Beide groepen volgden evenveel sessies, waarmee zowel een bias uit verschil in voorkeur als uit verschil in investering werd voorkomen. De kinderen die neurofeedback kregen gingen meer vooruit op gedrag zoals gerapporteerd door ouders en leerkrachten dan de kinderen die de aandacht training hadden gekregen (Gevensleben, Holl, Albrecht, Vogel, et al., 2009). Zelfs zes maanden na de training rapporteerden ouders beter gedrag voor de kinderen die neurofeedback volgden dan voor de kinderen die aandacht training hadden gekregen (Gevensleben et al., 2010). Helaas was bij deze meting slechts 70% van de gedragsvragenlijsten van de leerkrachten teruggekomen en waren deze daarom niet meegenomen als uitkomstmaat (Gevensleben et al., 2010). Een limitatie van deze studie is dat ze enkel betrekking heeft op kinderen met ADHD die geen stimulantia gebruiken. Op het moment dat gebruik van stimulantia geïndiceerd was, werden de kinderen niet opgenomen voor deelname in de studie of werden ze niet meegenomen voor de metingen na de interventieperiode. Op deze manier introduceert de studie een selectie bias, waarbij kinderen met mogelijk een ernstiger vorm van ADHD werden uitgesloten aan het begin van de studie en na de start van de studie werden de kinderen die meer last kregen van de ADHD-symptomen en dus medicatie nodig hadden uitgesloten.

Andere RCT studies hebben geprobeerd dit probleem met generaliseerbaarheid met betrekking tot het gebruik van stimulantia te voorkomen door neurofeedback behandeling te vergelijken met behandeling met stimulantia. De grootste van deze studies laat een gelijke vooruitgang in aandacht zien in gedrag gerapporteerd door ouders voor kinderen met ADHD die behandeld werden met neurofeedback (n=30), stimulantia (n=31) of een combinatie van neurofeedback en stimulantia (n=30) (Duric et al., 2012). Een kleinere studie laat vergelijkbare resultaten zien met een even grote vooruitgang in aandacht voor neurofeedback (n=12) als voor stimulantia (n=11) (Meisel et al., 2013). Opvallend is dat er een andere studie is die vooruitgang laat zien bij jongeren met ADHD

behandeld met stimulantia (*n*=15), maar niet voor degenen die neurofeedback kregen (*n*=14). Ook al lijken deze drie studies erg op elkaar in design van de studie, een groot verschil behelst het toegepaste medicatie protocol. De twee studies die gelijkwaardige vooruitgang laten zien voor neurofeedback en voor stimulantia (Duric et al., 2012; Meisel et al., 2013), hielden een standaard dosis voor medicatie aan gebaseerd op gewicht van 1 mg per kg lichaamsgewicht. Daarentegen maakte de studie waarbij stimulantia superieur was aan neurofeedback voor gedragsverbetering (Ogrim & Hestad, 2013), gebruik van een dubbel-blinde placebo-gecontroleerde titratie van medicatie, waarop vervolgens de dosis van de stimulantia individueel werd geoptimaliseerd. Titratie van stimulantia op basis van lichaamsgewicht wordt geregeld toegepast in onderzoek. Niet al het onderzoek echter, onderschrijft deze wijze van titratie van stimulantia (Greenhill et al., 2002; Rapport & Denney, 1997). Het is daarom mogelijk dat in de eerste twee studies stimulantia niet het optimale effect hebben gehad bij de jongeren met ADHD en de studie die de stimulantia individueel titreerde daarom als enige vond dat stimulantia effectiever zijn in het verminderen van ADHD-klachten dan neurofeedback. Verder onderzoek waarbij neurofeedback vergeleken wordt met stimulantia, getitreerd volgens een stapsgewijs dubbel-blind placebo-gecontroleerd protocol, is essentieel om te zien of neurofeedback behandeling als een gelijkwaardig alternatief van stimulantia kan worden toegepast in de klinische praktijk.

Tot op heden heeft geen van de dubbel-blinde onderzoeken verschil gevonden op gedragsuitkomsten tussen neurofeedback en placebo-neurofeedback (Arnold et al., 2013; Perreau-Linck et al., 2010; van Dongen-Boomsma et al., 2013). Tevens is er geen verschil gevonden tussen neurofeedback en placebo-neurofeedback op de neurocognitieve maten bij jongeren met ADHD (Arnold et al., 2013; Vollebregt et al., 2013) of gezonde studenten met relatief veel ADHD-achtige trekken (Logemann, Lansbergen, Van Os, Bocker, & Kenemans, 2010). Deze studies onderstrepen dat effecten uit de niet geblindeerde studies ook mogelijk het gevolg zijn van niet aan de behandeling gerelateerde specifieke effecten.

Neurofeedback protocollen zoals toegepast bij de gerandomiseerde studies zijn veel bediscussieerd. Zo is er verondersteld dat het automatisch laten aanpassen van grenswaarden door de computer met een bepaald tijdsinterval, mogelijk zorgt voor een minder effectieve training dan grenswaarden die handmatig worden aangepast (Lansbergen, van Dongen-Boomsma, Buitelaar, & Slaats-Willemse, 2011). Vergelijking van training met automatische grenswaarden en handmatig ingestelde grenswaarden resulteerde echter niet in verschillen op gedragsmatige uitkomsten (van Dongen-Boomsma et al., 2013). Verder is er gesteld dat het toepassen van expliciete leerstrategieën mogelijk noodzakelijk is om neurofeedback effectief te maken (Lansbergen et al., 2011). Het introduceren van meer actieve leerstrategieën aan het neurofeedback protocol resulteerde echter eveneens niet in meer positieve gedragsmatige uitkomsten voor neurofeedback (van Dongen-Boomsma et al., 2013). Een andere overweging heeft betrekking op de manier waarop de feedback over het EEG aan de jongeren wordt overgebracht: films (i.e. Duric et al., 2012; Ogrim & Hestad, 2013; van Dongen-Boomsma et al., 2013) of complexe grafische computer spelen (i.e. Arnold et al., 2013) zijn mogelijk afleidend van de eigenlijke neurofeedback training. Een vergelijking van

neurofeedback met simpele visuele feedback (*n*=11) met voor de jongere meer aantrekkelijke grafische computer spelen (*n*=11) bevestigt geen verschil in de manier waarop feedback wordt aangeboden (Palsson, Pope, Ball, Turner, & Nevin, 2001, March). De studie beschreven in dit proefschrift maakte gebruik van simpele visuele feedback. Ondanks de grafische verschillen tussen onze studie en die van Duric en collega's (2012), welke gebruik maakte van films of video spelen, waren beide studies niet in staat om bewijs te vinden voor aanvullende waarde van neurofeedback.

EEG frequentie training poogt om verschillende frequentiebanden te onderdrukken dan wel te versterken. Verschillende protocollen zijn toegepast in verschillende studies. Het "Lubar" protocol traint om theta te onderdrukken en SMR of beta activiteit te versterken, terwijl de patiënt in een ontspannen maar geconcentreerde staat is (Lubar, 2003; e.g. de studie uit dit proefschrift). Op deze manier wordt er gecontroleerd voor spierspanning welke snel terug te zien is in de hogere frequentiebanden. Andere studies passen training van theta/beta toe, met een correctie voor oogbewegingen (e.g. Gevensleben, Holl, Albrecht, Vogel, et al., 2009; de theta/beta training in deze studie was gecombineerd met training van slow cortical potentials). Als laatste zijn er studies die een geïndividualiseerd training protocol toepassen (i.e. Lansbergen et al., 2011) wat in de meeste gevallen neerkwam op training van theta/SMR (i.e.van Dongen-Boomsma et al., 2013). Het is mogelijk dat de effectiviteit van neurofeedback afhangt van het toegepaste training protocol. Op dit moment worden training protocollen echter afwisselend toegepast in de klinische behandel centra en in wetenschappelijk onderzoek. Er is geen consensus over de vorm van het trainingsprotocol de manier waarop deze uitgevoerd moet worden bij ADHD. Aanvullende kennis over specifieke werkingsmechanismen van neurofeedback op de hersenen is noodzakelijk, voordat neurofeedback protocollen op de juiste wijze kunnen worden aangepast voor de behandeling van psychiatrische stoornissen.

Neurofeedback heeft de intentie om EEG activiteit te trainen. Het is daarom opmerkelijk dat er nog geen robuuste veranderingen in EEG activiteit zijn gevonden na neurofeedback training. De studie van Gevensleben en collega's (2009) toont voor de jongeren die neurofeedback hebben gekregen een patroon waarbij het verschil in theta tussen de voor- en nameting lineair toeneemt van de voorkant van het hoofd naar de achterkant. Bij de groep die de aandacht training kreeg was dit patroon niet te zien. Ondanks het verschil in patroon van verschilscores, laat de studie geen verschil zien in frequentiebanden op specifieke elektroden. In het bijzonder ligt een significante daling in theta activiteit op Cz in de lijn der verwachting, bij uitvoer van een theta/beta training protocol met een elektrode geplaatst op Cz. Tevens waren er geen verschillen in beta tussen de jongeren die neurofeedback hadden gevolgd en de jongeren die aandacht training hadden gevolgd. Het theta/beta protocol is er op gericht om beta te verhogen en dus mag verwacht worden dat beta hoger is na de training dan voor de training. In tegenstelling daarmee verminderde beta mettertijd, vooral aan de voorkant van het hoofd. Deze vermindering was gerelateerd aan leeftijd en intelligentie en was onafhankelijk van de gekregen behandeling. Een andere studie die keek naar verschillen tussen voor en na neurofeedback training in frequentiebanden, kon eveneens geen verschillen in de frequentiebanden

vinden (Kropotov et al., 2007). Natuurlijk kan gezegd worden dat de verandering in hersenactiviteit ondergeschikt is aan het doel van de training om gedrag te verbeteren. Neurofeedback is echter gebaseerd op het idee dat (ADHD-) problemen voortkomen uit onder- of overactieve specifieke gedeelten van de hersenen. Deze over- of onder-activiteit wordt gemeten met een EEG opname in rust conditie met de ogen open en met de ogen dicht. Deze EEG opname kan vervolgens gebruikt worden om er een (individueel) training protocol op te baseren. Het lijkt logisch om veranderingen te verwachten na een interventie die frequentiebanden traint. Een mogelijke verklaring voor de afwezigheid van significante veranderingen in de frequentiebanden na de training is dat deze EEG opname plaatsvindt in rust condities (Arns et al., 2009; Gevensleben, Holl, Albrecht, Schlamp, et al., 2009). EEG opname in rust conditie lijkt in tegenspraak met de assumptie dat neurofeedback de hersenen probeert te trainen om meer flexibel en beter in staat te zijn hersenactiviteit te reguleren tijdens het uitvoeren van taken. Mogelijke veranderingen in hersenactivatie zijn dan onvermijdelijk duidelijker aanwezig tijdens het uitvoeren van taken. Het is inderdaad zo dat tijdens het uitvoeren van een aandacht taak verschillen zijn gevonden in ERP componenten (Kropotov et al., 2007; Wangler et al., 2011). Op dit moment hebben de andere grote gerandomiseerde studies (nog) niet gekeken naar veranderingen in de frequentiebanden voor jongeren die neurofeedback hebben gekregen en jongeren in de controle condities. Resultaten en verschillen van de frequentiebanden tussen de interventiegroepen zijn van belang om te kijken of het daadwerkelijk mogelijk is om frequentiebanden te trainen bij jongeren met ADHD.

Beide groepen adolescenten verbeterden evenveel op metingen van gedrag en neurocognitief functioneren. Het gebruik van stimulantia en het aanwezig zijn van comorbiditeit in de vorm van ASS bleek geen effect te hebben op de uitkomsten. In het eerste gedeelte van dit proefschrift hebben we verschillen beschreven met betrekking tot stimulantia en de aanwezigheid van een ASS diagnose naast ADHD. Daarbij kwam naar voren dat met ogen open en tijdens het uitvoeren van een taak de adolescenten met ADHD significant meer theta vertoonden dan adolescenten met een combinatie van ASS en ADHD. Een verhoging van theta en verlaging van beta activiteit bij ADHD (Cortese, 2012; Loo & Makeig, 2012; Snyder & Hall, 2006) is respectievelijk geassocieerd met verminderde waakzaamheid en verminderde aandacht (Banaschewski & Brandeis, 2007). Neurofeedback protocollen pogen daarom vaak om theta te verlagen en beta te verhogen. Als adolescenten met ASS+ADHD in beginsel minder theta activiteit vertonen dan adolescenten met ADHD, dan volgt daar logischerwijs uit dat vooruitgang van gedrag door het verlagen van theta activiteit door neurofeedback -indien mogelijk- minder duidelijk naar voren komt in adolescenten met ASS+ADHD, dan in adolescenten met ADHD zonder ASS comorbiditeit. Bij de huidige studie waren vooruitgang in cognitie en gedrag echter even groot voor beide diagnostische groepen. Evenzo laten jongeren met ADHD die stimulantia gebruiken minder theta activiteit zien dan jongeren met ADHD die geen stimulantia gebruiken (Clarke et al., 2002; Clarke et al., 2003; Hermens et al., 2005; Loo & Barkley, 2005) en zijn stimulantia effectief voor het verminderen van ADHD-symptomen (Faraone & Buitelaar, 2010; Greenhill et al., 2001) en voor het verbeteren van neurocognitief functioneren (Coghill et al.,

2013) bij jongeren met ADHD. Derhalve zouden verwachte verbeteringen door neurofeedback minder groot kunnen zijn bij jongeren die stimulantia gebruiken dan bij jongeren die geen stimulantia gebruiken. De resultaten van de huidige studie laten deze verschillen echter niet zien.

De hoofdvraag was of neurofeedback van aanvullende waarde is op de momenteel toegepaste standaard behandeling voor het verminderen van ADHD-symptomen bij jongeren met ADHD en bijkomende stoornissen. De huidige studie vond vooruitgang in gedrag en neurocognitief functioneren voor adolescenten met ADHD en comorbide stoornissen, direct na de interventieperiode en 1 jaar na de interventieperiode, onafhankelijk van de ontvangen behandeling. De afwezigheid van aanvullende lange termijn effecten van neurofeedback, gecombineerd met de afwezigheid van specifieke effecten van neurofeedback ten opzichte van placebo-neurofeedback (Arnold et al., 2013; Perreau-Linck et al., 2010; van Dongen-Boomsma et al., 2013; Vollebregt et al., 2013) en de intensiviteit van de behandeling met een groot aantal (20 tot 40) benodigde training sessies (Loo & Makeig, 2012), ondersteunen de implementatie van theta/SMR neurofeedback als behandeling voor adolescenten met ADHD en bijkomende stoornissen in de klinische praktijk niet.

CONCLUSIE

De hoofdconclusies van dit proefschrift zijn:

1. Resultaten suggereren dat er verschillen zijn in onderliggende hersenmechanismen gerelateerd aan ADHD-symptomatologie tussen adolescenten met ADHD en adolescenten met een combinatie van ASS en ADHD.
2. Theta/SMR neurofeedback laat geen aanvullend effect zien op de standaard behandeling om gedrag en neurocognitief functioneren te verbeteren bij adolescenten met ADHD en bijkomende stoornissen.

Samengenomen suggereren de studies uit dit proefschrift dat meer onderzoek nodig is naar de onderliggende psychofysiologie van ADHD-symptomatologie bij de combinatie van ASS+ADHD en ADHD. Begrip van psychofysiologische mechanismen die ten grondslag liggen aan ADHD-symptomatologie kan mogelijk helpen bij het ontwikkelen of verbeteren van interventies voor specifieke diagnostische groepen, zoals adolescenten met een combinatie van ASS+ADHD.

Neurofeedback was voorgesteld als een mogelijk effectieve interventie voor het verminderen van ADHD-symptomatologie. Theta/SMR neurofeedback had in dit onderzoek echter geen aanvullende waarde op de huidige standaard behandeling om gedrag of neurocognitief functioneren te verbeteren. De afwezigheid van aanvullende effecten op korte en langere termijn ondersteunen aldus niet de implementatie van theta/SMR neurofeedback als behandeling voor adolescenten met ADHD en bijkomende stoornissen in de klinische praktijk. Deze resultaten wijzen erop dat het gebruik van kennis over mogelijk onderliggende psychofysiologische mechanismen aan ADHD-symptomatologie voor de ontwikkeling van interventies om blijvende klinisch relevante gedragsveranderingen te bewerkstelligen een nog grotere uitdaging is dan de reeds complexe zoektocht naar psychofysiologische correlaten op zichzelf.

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CURRICULUM VITAE

Marleen Bink was born on October 11th, 1981 in Etten-Leur, the Netherlands. She enrolled at Tilburg University to study Psychology in 2003 and became fascinated by the interaction between physiology, cognition and behaviour and the possible implications for intervention research. For her bachelor research she investigated the effects of fish-oil on helplessness in students. In August 2006 she received her bachelor in Psychology with a major in Cognitive Neuroscience and a minor in Clinical Child and Adolescent Psychology. To focus her master on Clinical Neuropsychology, she transferred to Leiden University in September 2006. Under the supervision of prof. dr. Willem van der Does, she combined her interests for clinical neuropsychology and intervention research that resulted in the master thesis: The influence of omega-3 fatty acid on mood, heart rate variability and frontal lobe functioning in remitted depressed patients. Additionally, she worked during her master as a research assistant on projects to investigate cardiovascular reactivity as a result of in- and out-group bias at Leiden University, department of Social and Organizational Psychology. She completed her clinical internship at the psychiatric centre, GGz Haagstreek, department for rehabilitation of adults with acquired brain injury and psychiatric problems. After achieving her master in 2008, she started her PhD project at the Scientific centre for care and welfare (Tranzo), Tilburg University, that resulted in the present thesis.